


PDF hosted at the Radboud Repository of the Radboud University Nijmegen

The following full text is a publisher's version.

For additional information about this publication click this link.

<http://hdl.handle.net/2066/187343>

Please be advised that this information was generated on 2019-06-02 and may be subject to change.



Spinal (in)stability in metastatic bone disease

Experimental, computational,
and clinical perspectives

Karlijn Groenen

The work presented in this thesis was performed at the Orthopaedic Research Laboratory of the Radboud university medical center, Nijmegen and was carried out within the Radboud Institute for Health Sciences.

The publication of this thesis was kindly supported by:

Dutch Spine Society

Anna Fonds | NOREF

InSpine

© Karlijn Groenen. Nijmegen, 2018.

All rights reserved. No part of this thesis may be reproduced in any form without written permission of the author.

Cover design

Promotie In Zicht, Arnhem

Layout

Karlijn Groenen

Printing

Ipskamp Printing, Enschede

ISBN

978-94-92896-16-2

Spinal (in)stability in metastatic bone disease

Experimental, computational, and clinical perspectives

Proefschrift

ter verkrijging van de graad van doctor
aan de Radboud Universiteit Nijmegen
op gezag van de rector magnificus prof. dr. J.H.J.M. van Krieken,
volgens besluit van het college van decanen
in het openbaar te verdedigen
op dinsdag 17 april 2018
om 12.30 uur precies

door

Karlijn Hendrika Jacoba Groenen

geboren op 26 februari 1989
te Weert

Promotor

Prof. dr. ir. N.J.J. Verdonschot

Copromotoren

Dr. E.J.M. Tanck

Dr. Y.M. van der Linden (Leids Universitair Medisch Centrum)

Manuscriptcommissie

Prof. dr. J.H.A.M. Kaanders

Prof. dr. K. Ito (Technische Universiteit Eindhoven)

Dr. J.J. Verlaan (Universitair Medisch Centrum Utrecht)

Contents

Chapter 1	General introduction and outline	7
Chapter 2	The Dutch national guideline on metastases and hematological malignancies localized within the spine; a multidisciplinary collaboration towards timely and proactive management	29
Chapter 3	Clinical evaluation of the Spinal Instability Neoplastic Score in patients treated with radiotherapy for symptomatic spinal bone metastases	49
Chapter 4	Inducing targeted failure in cadaveric testing of 3-segment spinal units with and without simulated metastases	63
Chapter 5	Assessing spinal stability in metastatic bone disease: Comparing experimentally determined vertebral bone strength with predictions by experienced clinicians	81
Chapter 6	Case-specific non-linear finite element models to predict failure behavior in 3-segment spinal units	95
Chapter 7	Combining musculoskeletal and finite element modeling to predict spinal failure under physiological load cases. An exploratory study	117
Chapter 8	The effect of radiotherapy, and radiotherapy combined with bisphosphonates or RANK ligand inhibitors on bone quality in bone metastases. A systematic review	135
Chapter 9	General discussion and future perspectives	157
Chapter 10	Summary	175
Chapter 11	Samenvatting	183
Chapter 12	Dankwoord	191
	Curriculum Vitae	199
	List of publications	200
	PhD Portfolio	202



1

General introduction and outline

Cancer incidence

Every year, more than 100,000 people in the Netherlands are diagnosed with cancer [1]. Mainly due to the ageing population, the number of new cancer patients is projected to increase from 86,800 in 2007 to approximately 123,000 in 2020 [1]. These trends are also observed worldwide. The global number of new cancer cases is predicted to be over 20 million by 2030, compared with an estimated 12.7 million cases in 2008 [2, 3]. At the same time, earlier detection of cancer and more effective cancer treatments reflect a better prognosis [1].

Increasing cancer incidence rates together with longer survival result in more cancer patients being confronted with metastatic disease during follow-up. In metastases, cancer cells separate from the site of the primary tumor, migrate via the blood or lymph system to other tissues, where they settle and grow [4, 5]. For patients the diagnosis of metastases is calamitous, as in metastatic cancer, when widespread, cure is no longer possible [6]. Depending on the primary tumor, performance, and extension of disease, survival may range from weeks, months, to several years [7]. Mostly, a palliative trajectory is offered, with local and systemic anticancer treatments aimed at prolonging life, or at prevention and relief of disease-related symptoms and with emphasis on the best possible quality of life. In case of solitary (a single metastasis) or oligometastatic (<4-5 metastases) disease, sometimes extended survival or even cure is possible. Widespread metastases are the primary cause of death in patients with cancer [8, 9].

Bone metastases

Bone is the third most frequent site where metastases are found, following the lungs and liver [10]. Bone metastases occur in almost all cancer types, with prostate, breast and lung cancer most frequently implicated [11, 12]. Once resident in bone, metastatic tumor cells have the ability to interfere with normal bone remodeling processes, resulting in destructive bone lesions. Bone metastases can be classified as osteolytic, osteoblastic, or mixed, according to the primary mechanism of interference with normal bone remodeling and subsequent appearances on diagnostic imaging [13, 14] (Figure 1). When bone resorption predominates with little or no new bone formation, local bone destruction occurs and the metastases have a lytic appearance [13, 15]. This is, among others, mostly the case in breast, lung, thyroid, renal, and gastrointestinal malignancies [11, 16]. By contrast, bone metastases characterized by an increase in osteoblast activity appear largely blastic (or sclerotic), characterized by deposition of new bone [13]. In particular, bone metastases from prostate cancer are especially blastic, but breast and lung cancer can also give rise to blastic lesions [11, 16]. A mixed lesion contains both osteolytic and osteoblastic components, and is for example seen in breast cancer and gastrointestinal cancers [16].



Figure 1 Spinal bone metastases on medical imaging: (a) Whole body bone scan using bone scintigraphy showing extensive osseous metastases involving multiple levels in the thoracic spine, lumbar spine, and sacrum. There are multiple metastases in the rib cage, bilateral bony pelvis and both scapulae; (b) Lytic lesions and a severely collapsed vertebral body (both in white circle) in the spine on a computed tomography (CT) scan; (c) Blastic lesions throughout the full spine on a CT scan. The blastic lesions represent on CT scan as bright spots, of which one is detailed in the zoomed image.

Source bone scintigraphy: <http://www.hkma.org/english/cme/onlinecme/cme200211main.htm>

Bone metastases most commonly affect the axial skeleton, with the vertebrae, ribs and pelvis as frequently involved sites, reflecting the preference for tumor cells to metastasize in vascularized skeletal parts [11] (Figure 1). Within the axial skeleton, the spinal column is the most frequent site of metastases, affecting up to 70% of patients with bone metastases [12, 15, 17, 18]. The thoracic vertebrae are frequently involved sites (60 - 75%), followed by lumbar (15 - 30%) and cervical vertebrae (<10%) [7, 19, 20]. Anatomically, metastases in the spinal column can be classified as intradural (intradural or extradural) or extradural (95%) [21]. The extradural lesions can be divided into pure epidural lesions, which are rare, and those arising initially from the vertebra, but migrating to the thecal sac [22, 23] (Figure 2).

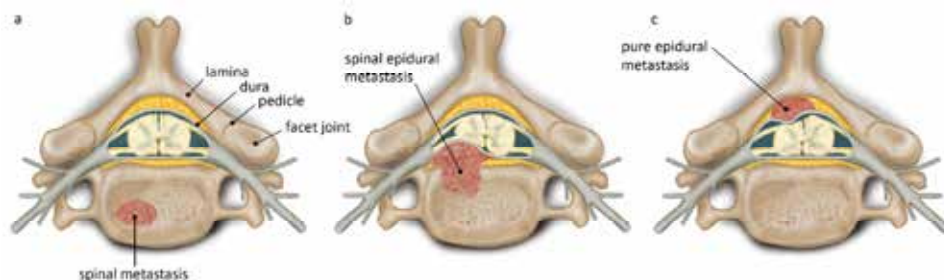


Figure 2 Schematic figure showing metastases in the spinal column. (a) Spinal bone metastasis restricted to the vertebral body; (b) Extradural spinal bone metastasis originating from the vertebral body grown into the epidural space, which might result into compression of neural structures; and (c) Pure epidural metastasis (vertebra not affected).

Source: Adapted from Van Kessel et al., *Ned Tijdschr Geneesk.* 2013;157:A5331.

Spinal bone metastases: Clinical implications

For patients, the presence of spinal bone metastases may cause a range of complications, all impairing their quality of life. Clinically, back pain is the most frequently reported symptom [23-25]. Systemically, spinal bone lesions can lead to hypercalcemia and anemia, due to metastatic tissue infiltrating the bone marrow. Locally, spinal bone lesions may jeopardize the mechanical integrity of bone, thereby putting the patients at increased risk of developing spinal instability, (progressive) deformity, and/or pathological fractures [26]. Bone deformities or fractures may be devastating for patients with spinal bone metastases, as they can be accompanied by pain, stress and anxiety, potential need for radiotherapy and/or surgery, decreased quality of life, and can lead to debilitating complications such as nerve root or spinal cord compression (Figure 3). A randomized study of 342 patients showed that about 3% of the patients with spinal bone metastases eventually show signs of metastatic spinal cord compression (MSCC) [27]. Although the risk of developing neurological deficits is relatively low, it is one of the most dreaded complications of metastatic cancer. If left untreated, MSCC usually causes relentless and progressive pain, paralysis, sensory loss and urinary and bowel incontinence [24]. All such adverse events dramatically affect the mobility and self-care of patients with an already limited life expectancy (median life expectancy of patients entering radiotherapy studies on bone metastases is about seven months [27]). Therefore, such adverse events should be prevented as much as possible [26, 28, 29].

Due to the increasing overall cancer incidence, prolonged survival of patients with cancer, and the spine being the preferred site of metastatic bone disease, a rise in incidence of spinal bone metastases is observed. The combination with the severity of the possible complications related to spinal bone metastases makes the presence of spinal bone metastases a growing problem.



Figure 3 Magnetic resonance (MR) images of a patient suffering from multiple myeloma. Figures a and b show progression of the lesion causing vertebral collapse and clinical MSCC (total paraplegia) (affected vertebrae are shown in the white circles). The MRI scan shown in (b) has been acquired approximately one year after the scan shown in (a).

Treatment of spinal bone metastases

Current management of spinal bone metastases focuses on optimizing quality of life of the patient by providing effective pain relief and preserving or restoring, if necessary, neurological function and mobility [23, 30]. In addition to pain medication, local radiotherapy is widely accepted as the standard of care for palliative treatment of patients with painful bone metastases, including symptomatic (with pain and/or neurological problems) spinal bone metastases [31, 32]. Radiotherapy is non-invasive, as opposed to surgery, and effective in achieving pain reduction in around 60 - 70% of patients [30, 33-38]. In addition, single fraction radiotherapy has shown to be equally effective as multi-fraction palliative radiotherapy in terms of pain response [33, 36-38]. Therefore, single fraction radiotherapy is considered to be more convenient from a patient perspective and is less costly to society [39, 40].

The outcome of radiotherapy for neurological complaints depends on the patient's pre-treatment neurological status. Starting treatment when a patient is still able to walk results in the highest chance of retaining the ambulatory status [41]. However, if

treatment begins when a patient is already bedridden, the chance of this patient regaining his/her walking ability is limited [41]. Consequently, timely diagnosis, prompt therapy, and follow-up are of the utmost importance, so that especially progression of spinal metastases towards irreversible neurological deficits may be prevented as much as possible.

A limitation of radiotherapy is the relatively low dose tolerance of critical adjacent organs at risk, such as the spinal cord and the gastrointestinal tract, which is about 50-60 Gy₂ [42]. This is a potential problem when a patient already received high curative doses for the primary tumor when located adjacent to the spinal column, and is in need of repetitive courses of palliative radiotherapy during the disease trajectory. The recent development of highly advanced radiation technologies, however, has enabled new radiotherapy techniques that permit high and precise dose delivery within the target while minimizing dose to the surrounding healthy tissue, including the spinal cord (e.g. stereotactic radiosurgery (SRS), stereotactic body radiotherapy (SBRT), intensity modulated radiotherapy (IMRT)) [43, 44]. Besides delivery of adequate doses for pain relief in patients already irradiated, in some patients an additional goal of such advanced radiotherapy techniques is to deliver doses to destroy the metastasis and achieve permanent local control [44, 45]. Hence, these advanced radiotherapy techniques may not only reduce pain, but have the potential to result in higher local control rates, thereby also preventing progression to MSCC.

In addition to pain reduction, preserving or restoring spinal stability is an important goal in spinal bone metastases treatment. The use of radiotherapy in order to stabilize affected bones is based mostly on clinical experience. Radiotherapy is thought to first reduce the bone mineral density (BMD) during a short period of time directly after radiotherapy, but subsequently induce re-calcification of the lesion, a process during which new bone is formed [46]. It is generally believed that, in patients responding to radiotherapy, about three months are necessary for the bone to be sufficiently strengthened [46]. Although the clinical experience is abundant, scientific data underlining this stabilizing effect are scarce.

In contrast to radiotherapy, surgery is the preferred treatment in case of progressive spinal instability, as surgical osteosynthesis provides immediate stabilization. In addition to the more invasive procedures involving open fixation, minimally invasive approaches are increasingly being used [47] (Figure 4). For surgery to be an option, a life expectancy of at least three months, a good clinical condition of the patient, and a limited area of metastatic damage and/or obstruction so that surgery is possible from a technical point of view are required [31].

For pure MSCC, surgery and radiotherapy are considered equivalent options [31, 48]. In current clinical practice, the vast majority of patients are treated using radiotherapy. A large study comprising a cohort of 1043 patients with spinal bone metastases showed that only 5% of the patients received surgery, whereas 95% was treated using radiotherapy [7]. The main reasons for this small percentage of patients

being surgically treated are an insufficient clinical condition, limited life expectancy, too many vertebrae (severely) affected leading to the fact that surgical treatment is not an option, and, most importantly, non-invasive radiotherapy being largely effective in pain reduction.



Figure 4 Postoperative X-ray of a patient suffering from an L2 metastasis from lung cancer. The spine was surgically treated with vertebroplasty (V) and percutaneous internal fixation using screws.

Source: Adopted from Laredo et al. Joint Bone Spine. 2017; May 9.

Patients are often treated with a combination of local radiotherapy and systemic treatments. These systemic treatments include e.g. anticancer treatments with chemotherapy or hormonal therapy, bisphosphonates, and receptor activator of nuclear factor kappa- β ligand (RANKL) inhibitors (e.g. denosumab). Bisphosphonates and RANKL inhibitors are bone targeted therapies, used to increase the bone mass and strength, thereby potentially stabilizing the affected bone and prevent future pathological fractures [49-54]. In contrast, other anticancer treatments, such as chemotherapy and hormonal therapy, attack tumor cells located in all organs and structures throughout the body, thereby decreasing the lesion's size and allowing bone to restore.

Care until now is mostly reactive, acting when patients present themselves with complaints. Optimally, selecting the best treatment modality then requires a multidisciplinary approach employing specialists in spine surgery, systemic treatment and radiotherapy. Since more and more patients are confronted with the complications of spinal bone metastases and have a prolonged life expectancy, clinical guidelines increasingly pursue a proactive rather than reactive care management, directed at preventing complications instead of responding to clinical symptoms only [31]. Moreover, treatment decision making is not only based on the expected treatment

outcome, but also depends on values and preferences of the patient ('shared decision making'), the patient's prognosis, estimated survival, and estimated spinal instability [31]. In summary, treatment decision making in patients with spinal bone metastases is a highly complex process.

Spinal instability

Estimating spinal instability plays an increasingly important role in treatment decision making, as it can be the source of back pain and has been recommended as an indication for surgery [31, 55]. Multiple definitions of spinal instability exist, of which most origin from the definition postulated by White and Panjabi. In 1978, White and Panjabi defined clinical instability in the spine as 'the loss of the ability of the spine under physiological loads to maintain relationships between vertebrae in such a way that there is neither damage nor subsequent irritation to the spinal cord or nerve roots, and, in addition, there is no development of incapacitating deformity or pain due to structural changes' [56]. More recently, the Spinal Oncology Study Group formulated a definition specifically for the metastatically affected spine. They postulated metastatic spinal instability as the 'loss of spinal integrity as a result of a neoplastic process that is associated with movement-related pain, symptomatic or progressive deformity, and/or neural compromise under physiological loads' [57].

Despite these definitions, the absence of validated guidelines or an established predetermined set of risk factors makes that clinicians are having difficulties in assessing spinal instability based on available diagnostic imaging data [57]. As a result, clinicians mostly rely on their clinical experience to assess which patients will experience progressive spinal instability and which will not.

Methods to assess spinal instability

Finding an objective measure for assessing spinal instability has been under study for several decades. For example, tumor size, location of the lesion, radiological appearance, bone density, and pre-existing deformities have been analyzed to prognosticate for spinal instability [58-62]. Unfortunately, on the basis of these individual risk factors a powerful predictor for the degree of spinal instability could not yet be formulated. Hence, choosing the optimal local treatment, i.e. radiotherapy and/or surgery, based on these instability predictors is limited, and thus remains based upon individual experience of involved clinicians.

Over the years, various classification systems have been proposed to elucidate spinal instability and its clinical consequence, i.e. how does the radiological findings translate into clinical symptoms, momentarily and in the near future. For example, Denis developed the 3-column concept to radiologically determine the presence or absence of spinal instability due to traumatic injuries [63, 64]. This 3-column concept divides the

vertebral column into three columns: the anterior (anterior half of the vertebral body, the anterior longitudinal ligament, and the anterior half of the intervertebral (IV) disc), middle (posterior half of the vertebral body and IV disc, and the posterior longitudinal ligament), and posterior (spinous processes, facet joints, laminae, pedicles, and the intra- and supraspinal ligament) column. Mechanical instability was defined to be occurring when two of the three columns were affected. However, spinal instability due to neoplasia differs significantly from high-energy traumatic injuries in the pattern of bony and ligamentous involvement, potential for healing, neurologic manifestations, and bone quality. Therefore, the extrapolation of the 3-column concept to oncologic patients is debatable and not straightforward [57]. Hence, spinal instability as the result of a neoplastic process requires a specific and different set of criteria for stability assessment [57, 65].

In addition, Taneichi et al. [66] have analyzed radiological and clinical data obtained in 53 patients with 100 thoracic or lumbar metastases by using a multivariate logistic regression model in an attempt to establish the criteria of impending vertebral body collapse. They found the following criteria for impending collapse: 50 - 60% involvement of the vertebral body with no destruction of other structures or 25 - 30% involvement of the vertebral body with costovertebral joint destruction in the thoracic spine (Th1 to Th10); and 35 - 40% involvement of vertebral body or 20 - 25% involvement of the vertebral body with posterior elements destruction in thoracolumbar and lumbar spine (Th11 to L5). A major limitation of this study, however, was that only tumor size and location of defects within the vertebrae were considered; other important factors, such as bone density, were not analyzed [55].

In 2010, the Spinal Oncology Study Group, an international group of 30 spine oncology experts introduced the first consensus-based guideline that attempts to register spinal instability due to metastatic disease: the Spinal Instability Neoplastic Score (SINS) [57]. The SINS uses one patient related factor (pain) and five radiological parameters (location, type of lesion, spinal alignment, vertebral body collapse, and posterolateral involvement of spinal elements) determined from computed tomography (CT) image data. Scores varying from 0 to 4 points are given to each parameter. Sum scores subsequently classify the spinal column as stable (0 - 6 points), potentially unstable (7 - 12 points), or unstable (13 - 18 points). Surgical consultation is recommended for patients with a spinal column classified as either potentially unstable or unstable. As such, the SINS aims to facilitate interdisciplinary communication, assess and categorize spinal instability, and optimize treatment decision making. Although previous studies have already shown that the SINS has a moderate to excellent inter-observer and intra-observer reliability [67-71], it is still unclear whether the SINS has sufficient predictive power to assess progressive spinal instability [59, 61, 62, 72-75]. For the SINS to be useful in clinical practice, this predictive power is, however, indispensable and, therefore, warrants further research. Nevertheless, the SINS could be used as a tool to facilitate multidisciplinary communication [76].

Finite element models to assess spinal instability

Spinal instability is determined by a complex interplay of various factors that often vary over time. Therefore, it might be difficult to comprehend and hard to capture spinal instability in a set of simple guidelines. Computationally based, non-invasive assessment of spinal instability and vertebral strength is an alternative approach. Finite element (FE) analysis is an advanced computer technique of structural stress analysis developed in engineering mechanics and has found applications in bone mechanics. CT based FE models calculate bone strength using case specific geometrical and material parameters, thereby not only accommodating for parameters related to lesion and patient, but also covering additional aspects that affect the fracture risk, such as the initial strength of the bone and the daily loads applied to the bone.

Several studies have already demonstrated that FE models can accurately predict compressive vertebral stiffness and strength, when compared to *in vitro* experiments (stiffness: $R^2 = 0.50 - 0.81$ [77-83]; strength: $R^2 = 0.76 - 0.96$ [77, 78, 81-88]). However, these models only comprise single vertebrae. The simplified loading conditions applied to single vertebrae are bound to introduce loading artifacts. A more physiological loading condition can be obtained by using 3-segment spinal units, consisting of three consecutive vertebrae and two intervertebral discs (IVDs). In this way, the (middle) target vertebra is loaded via two IVDs, the posterior elements, and the spinal ligaments.

In addition, there is limited research on the development of experimentally validated FE models to study or predict failure behavior in metastatically affected vertebrae. The work by Whyne et al. [89-91] and Tschirhart et al. [92, 93] studied the influence of tumor growth, but their FE models did not account for the effects of the heterogeneity in mineral density of the bone tissue, which is known to have a significant influence on vertebral body strength. In contrast, the models by Mirzaei et al. [88], Matsuura et al. [80], and Sahli et al. [94] did account for heterogeneous bone properties when predicting stiffness and strength. Nevertheless, Matsuura et al. [80] and Sahli et al. [94] applied equations relating BMD and material properties based on human vertebrae to porcine vertebrae, which might have introduced errors. Moreover, mechanical stability and micro-damage formation in rats has been evaluated using micro-CT (μ CT) based FE models [95, 96]. Micro-CT is, however, not yet possible in a clinical setting. Although Mirzaei et al. [88] developed case-specific FE models based on clinical CT scans and were able to accurately predict vertebral strength ($R^2 = 0.84$), their model was restricted to single vertebral bodies.

During the past years, a workflow for generating case-specific FE models of metastatic femora for predicting bone strength has been developed and validated within our Orthopaedic Research Laboratory [97, 98]. In addition, these FE models showed to improve the prediction of bone strength of metastatic femora in comparison to the strength prediction by experienced clinicians [97]. Within the context of this thesis, the workflow developed for the femur was applied to the spine and, subsequently, optimized. In short, case-specific FE models are based on quantitative CT (qCT) scans,

from which the bone geometry and quality are extracted [99]. Mechanical properties are calculated from the bone mineral density and are then assigned to the FE model [99]. Subsequently, a loading condition is applied and the load as well as location at which the bone fails can be calculated.

Musculoskeletal modeling

In the stage of developing an FE model, the initial loading regime should be straightforward so that mechanical experiments can be reliably mimicked in the FE simulations, thereby experimentally validating the model. Such simplified load cases resemble for example upright standing. However, these simple load cases do not resemble the loads imposed on the spine during daily life activities and might, therefore, be suboptimal for *in vivo* fracture risk predictions. In fact, various loading scenarios (e.g. forward flexion, lateral bending, or axial rotation) have been demonstrated to affect the risk of burst fracture initiation in the metastatically affected spine [100]. Therefore, a more sophisticated loading regime is required.

The loads acting on the spine *in vivo* are a complex combination of body weight, ligaments, and muscle forces. Incorporating joint contact forces and muscle forces into the loading profile results in a more physiological loading condition. These forces could be determined using musculoskeletal modeling. Musculoskeletal models apply mechanical principles to a system composed of bones, muscles and ligaments in order to calculate joint contact forces and muscle forces during different activities. As such, the load imposed on the spine during daily activities, such as holding or lifting an object, can be determined. This sophisticated loading regime could then be applied to patient-specific FE models.

Aim and outline of this thesis

The goal of this thesis was to improve the assessment of spinal (in)stability in metastatic spinal bone disease and, as a consequence, the multidisciplinary care for patients with spinal bone metastases. The following outline describes the different aspects of this thesis in more detail.

Chapter 2 describes the results of an evidence-based approach to develop a Dutch national guideline on metastases and hematological malignancies localized in the spine. Goals were to create a comprehensive guideline focusing on proactive management, with a strong focus on the perspective of patients, with treatment recommendations weighing life expectancy and expected outcome. The guideline is applicable in daily practice and provides an up to date and concise overview of diagnostics and treatment possibilities for these patients suffering from an entity with serious impact on the quality of life. In addition, suggestions on implementation with practical considerations for

hospitals on how to organize care are discussed. The crucial role of patients in decision making is emphasized in this guideline.

Chapter 2 demonstrated that assessing spinal instability is an important part of treatment decision making in patients with spinal bone metastases. The recently introduced SINS is a clinical guideline that aims to objectively assess spinal instability in patients with spinal bone metastases. The aim of **Chapter 3** was to evaluate the predictive value of the total and individual components of the SINS system for spinal instability in a cohort of patients with cancer and spinal bone metastases, treated with radiotherapy. Furthermore, the inter-observer agreement of both the total categorical SINS score and the individual components was determined.

Another approach for assessing spinal instability is the use of subject specific FE models. Therefore, this thesis aimed to develop and optimize a workflow for generating subject-specific FE models, to validate it against mechanical experiments, and show its clinical application in actual patient data. For these purposes, mechanical experiments were performed in which cadaveric 3-segment spinal units with and without simulated metastatic lesions were destructively tested in axial compression. Vertebral bone strength was subsequently determined (**Chapter 4**).

To be clinically relevant, not only should the FE model predict failure loads in agreement with the experimentally measured failure loads, it should also improve upon current clinical practice. In **Chapter 5**, the aim was to assess how accurate experienced clinicians are at predicting the strength of vertebrae with simulated metastatic lesions, as measured *in vitro*. For this, clinicians were asked to rank vertebrae tested in Chapter 4 on bone strength. Subsequently, the rankings by the clinicians were compared with the experimental ranking. Moreover, it was tested what imaging modality - magnetic resonance imaging (MRI), CT, and/or dual-energy X-ray absorptiometry (DEXA) - provided the best predictions and the inter-observer agreement was analyzed.

In a next step, the mechanical experiments were mimicked in FE simulations to predict vertebral strength (**Chapter 6**).

One of the main goals of this work was to further improve our understanding on the prediction of spinal instability in patients with cancer and spinal bone metastases. In **Chapter 7** we demonstrated the workflow developed in Chapter 6 to a patient case from an ongoing prospective patient study (RACOST, ClinicalTrials.gov Identifier: NCT02407795) [101]. Patients enrolled in this randomized phase III study received conventional or stereotactic radiotherapy to treat painful spinal bone metastases, and were followed during and after treatment. Some of the patients in this study sustained an unexpected pathological fracture in the vertebrae during follow-up. In the exploratory study described in Chapter 7, we clinically implemented the workflow to assess vertebral strength in an actual patient. We combined musculoskeletal and FE modeling and aimed to demonstrate whether modeling physiological load cases instead of a simple loading regime can significantly affect the fracture risk prediction.

Immediate stabilization of the affected vertebrae can be achieved by surgical osteosynthesis in patients with cancer and spinal bone metastases. From the perspective of the patient, however, it would be beneficial if metastatic lesions could be sufficiently stabilized, if necessary, using non-invasive treatments, such as local radiotherapy and/or systemic treatments. The clinical experience is that in most patients treated with radiotherapy, either or not in combination with systemic treatments such as bisphosphonates, the clinical gain is sufficient in the light of limited life expectancy and often re-calcification is observed on follow-up imaging. However, it is unclear how these observations affect spinal instability. Therefore, **Chapter 8** describes a systematic literature study to assess the effect of radiotherapy, either or not combined with bisphosphonates and/or RANKL inhibitors, on bone quality and bone strength parameters in bone metastases originating from solid tumors.

A general discussion and summary of the results of this thesis will be provided in **Chapter 9** and **Chapter 10**, respectively.

References

1. Signaleringscommissie Kanker van KWF Kankerbestrijding. Kanker in Nederland tot 2020. Trends en prognoses. Amsterdam: KWF Kankerbestrijding, 2011.
2. Bray F, Jemal A, Grey N, Ferlay J, Forman D. Global cancer transitions according to the Human Development Index (2008-2030): a population-based study. *Lancet Oncol* 2012;13(8):790-801.
3. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer* 2010;127(12):2893-2917.
4. Seyfried TN, Huysentruyt LC. On the origin of cancer metastasis. *Crit Rev Oncog* 2013;18(1-2):43-73.
5. Woodhouse EC, Chuaqui RF, Liotta LA. General mechanisms of metastasis. *Cancer* 1997;80(8 Suppl):1529-1537.
6. Laitinen M, Ratasvuori M, Pakarinen TK. The multi-model approach to metastatic disease. European Instructional Lectures. Berlin. Springer Berlin Heiderlberg, 2012:35-44.
7. Bollen L, van der Linden YM, Pondaag W, Fiocco M, Pattynama BP, Marijnen CA, Nelissen RG, Peul WC, Dijkstra PD. Prognostic factors associated with survival in patients with symptomatic spinal bone metastases: a retrospective cohort study of 1,043 patients. *Neuro Oncol* 2014;16(7):991-998.
8. Weigelt B, Peterse JL, van 't Veer LJ. Breast cancer metastasis: markers and models. *Nat Rev Cancer* 2005;5(8):591-602.
9. Chaffer CL, Weinberg RA. A perspective on cancer cell metastasis. *Science* (80-) 2011;331(6024):1559-1564.
10. Van der Linden Y, Hoskin P. Bone metastases. In: Carsten Nieder C, Langendijk JA, eds. Re-irradiation: New frontiers. Berlin. Springer, 2011:191-204.
11. Coleman RE. Skeletal complications of malignancy. *Cancer* 1997;80(8 Suppl):1588-1594.
12. Steenland E, Leer JW, van Houwelingen H, Post WJ, van den Hout WB, Kievit J, de Haes H, Martijn H, Oei B, Vonk E, van der Steen-Banasik E, Wiggensraad RG, Hoogenhout J, Warlam-Rodenhuis C, van Tienhoven G, Wanders R, Pomp J, van Reijn M, van Mierlo I, Rutten E. The effect of a single fraction compared to multiple fractions on painful bone metastases: a global analysis of the Dutch Bone Metastasis Study. *Radiother Oncol* 1999;52(2):101-109.
13. Makhoul I, Montgomery CO, Gaddy D, Suva LJ. The best of both worlds - managing the cancer, saving the bone. *Nat Rev Endocrinol* 2016;12(1):29-42.
14. Selvaggi G, Scagliotti GV. Management of bone metastases in cancer: a review. *Crit Rev Oncol Hematol* 2005;56(3):365-378.
15. Coleman RE. Metastatic bone disease: clinical features, pathophysiology and treatment strategies. *Cancer Treat Rev* 2001;27(3):165-176.
16. Macedo F, Ladeira K, Pinho F, Saraiva N, Bonito N, Pinto L, Goncalves F. Bone Metastases: An Overview. *Oncol Rev* 2017;11(1):321.
17. Kakhki VR, Anvari K, Sadeghi R, Mahmoudian AS, Torabian-Kakhki M. Pattern and distribution of bone metastases in common malignant tumors. *Nucl Med Rev Cent East Eur* 2013;16(2):66-69.
18. Sciubba DM, Petteys RJ, Dekutoski MB, Fisher CG, Fehlings MG, Ondra SL, Rhines LD, Gokaslan ZL. Diagnosis and management of metastatic spine disease. A review. *J Neurosurg Spine* 2010;13(1):94-108.
19. Helweg-Larsen S, Sorensen PS, Kreiner S. Prognostic factors in metastatic spinal cord compression: a prospective study using multivariate analysis of variables influencing survival and gait function in 153 patients. *Int J Radiat Oncol Biol Phys* 2000;46(5):1163-1169.
20. Sorensen S, Borgesen SE, Rohde K, Rasmusson B, Bach F, Boge-Rasmussen T, Stjernholm P, Larsen BH, Agerlin N, Gjerris F, et al. Metastatic epidural spinal cord compression. Results of treatment and survival. *Cancer* 1990;65(7):1502-1508.
21. Perrin RG, Laxton AW. Metastatic spine disease: epidemiology, pathophysiology, and evaluation of patients. *Neurosurg Clin N Am* 2004;15(4):365-373.
22. Jacobs WB, Perrin RG. Evaluation and treatment of spinal metastases: an overview. *Neurosurg Focus* 2001;11(6):e10.

23. Bartels RH, van der Linden YM, van der Graaf WT. Spinal extradural metastasis: review of current treatment options. *CA Cancer J Clin* 2008;58(4):245-259.
24. Loblaw DA, Perry J, Chambers A, Laperriere NJ. Systematic review of the diagnosis and management of malignant extradural spinal cord compression: the Cancer Care Ontario Practice Guidelines Initiative's Neuro-Oncology Disease Site Group. *J Clin Oncol* 2005;23(9):2028-2037.
25. Perrin RG. Metastatic tumors of the axial spine. *Curr Opin Oncol* 1992;4(3):525-532.
26. Costa L, Badia X, Chow E, Lipton A, Wardley A. Impact of skeletal complications on patients' quality of life, mobility, and functional independence. *Support Care Cancer* 2008;16(8):879-889.
27. Van der Linden YM, Dijkstra SP, Vonk EJ, Marijnen CA, Leer JW, Dutch Bone Metastasis Study G. Prediction of survival in patients with metastases in the spinal column: results based on a randomized trial of radiotherapy. *Cancer* 2005;103(2):320-328.
28. Sutcliffe P, Connock M, Shyangdan D, Court R, Kandala NB, Clarke A. A systematic review of evidence on malignant spinal metastases: natural history and technologies for identifying patients at high risk of vertebral fracture and spinal cord compression. *Health Technol Assess* 2013;17(42):1-274.
29. Harel R, Angelov L. Spine metastases: current treatments and future directions. *Eur J Cancer* 2010;46(15):2696-2707.
30. Falkmer U, Jarhult J, Wersall P, Cavallin-Stahl E. A systematic overview of radiation therapy effects in skeletal metastases. *Acta Oncol* 2003;42(5-6):620-633.
31. Integraal Kanker Centrum Nederland. Oncoline Richtlijnen oncologische zorg - Wervelmetastasen. Last accessed. Available from: <http://www.oncoline.nl/wervelmetastasen>.
32. Lutz S, Balboni T, Jones J, Lo S, Petit J, Rich SE, Wong R, Hahn C. Palliative radiation therapy for bone metastases: Update of an ASTRO Evidence-Based Guideline. *Pract Radiat Oncol* 2017;7(1):4-12.
33. Chow E, Harris K, Fan G, Tsao M, Sze WM. Palliative radiotherapy trials for bone metastases: a systematic review. *J Clin Oncol* 2007;25(11):1423-1436.
34. Chow E, van der Linden YM, Roos D, Hartsell WF, Hoskin P, Wu JS, Brundage MD, Nabid A, Tissing-Tan CJ, Oei B, Babington S, Demas WF, Wilson CF, Meyer RM, Chen BE, Wong RK. Single versus multiple fractions of repeat radiation for painful bone metastases: a randomised, controlled, non-inferiority trial. *Lancet Oncol* 2014;15(2):164-171.
35. Maranzano E, Trippa F, Casale M, Costantini S, Lupattelli M, Bellavita R, Marafioti L, Pergolizzi S, Santacaterina A, Mignogna M, Silvano G, Fusco V. 8Gy single-dose radiotherapy is effective in metastatic spinal cord compression: results of a phase III randomized multicentre Italian trial. *Radiother Oncol* 2009;93(2):174-179.
36. Sze WM, Shelley M, Held I, Mason M. Palliation of metastatic bone pain: single fraction versus multifraction radiotherapy - a systematic review of the randomised trials. *Cochrane Database Syst Rev* 2004(2):CD004721.
37. Wu JS, Wong R, Johnston M, Bezjak A, Whelan T, Cancer Care Ontario Practice Guidelines Initiative Supportive Care G. Meta-analysis of dose-fractionation radiotherapy trials for the palliation of painful bone metastases. *Int J Radiat Oncol Biol Phys* 2003;55(3):594-605.
38. Chow E, Zeng L, Salvo N, Dennis K, Tsao M, Lutz S. Update on the systematic review of palliative radiotherapy trials for bone metastases. *Clin Oncol (R Coll Radiol)* 2012;24(2):112-124.
39. Konski A, James J, Hartsell W, Leibenhaut MH, Janjan N, Curran W, Roach M, Watkins-Bruner D. Economic analysis of radiation therapy oncology group 97-14: multiple versus single fraction radiation treatment of patients with bone metastases. *Am J Clin Oncol* 2009;32(4):423-428.
40. van den Hout WB, van der Linden YM, Steenland E, Wiggendaad RG, Kievit J, de Haes H, Leer JW. Single-versus multiple-fraction radiotherapy in patients with painful bone metastases: cost-utility analysis based on a randomized trial. *J Natl Cancer Inst* 2003;95(3):222-229.
41. Rades D, Douglas S, Huttenlocher S, Rudat V, Veninga T, Stalpers LJ, Basic H, Karstens JH, Hoskin PJ, Adamietz IA, Schild SE. Validation of a score predicting post-treatment ambulatory status after radiotherapy for metastatic spinal cord compression. *Int J Radiat Oncol Biol Phys* 2011;79(5):1503-1506.

42. Baumann M, Begg AC, Bentzen SM, Dorr W, Gregoire V, Haustermans K, Horsman MR, Joiner MC, Koritzinsky M, Lee J, Overgaard J, Steel GG, Stewart FA, Trott KR, van der Kogel AJ, Wouters BG, Zips D. *Basic Clinical Radiobiology*. 4th ed. London, Great Britain: Hodder Arnold, 2009.
43. Sahgal A, Roberge D, Schellenberg D, Purdie TG, Swaminath A, Pantarotto J, Filion E, Gabos Z, Butler J, Letourneau D, Masucci GL, Mulroy L, Bezjak A, Dawson LA, Parliament M, The Canadian Association of Radiation Oncology-Stereotactic Body Radiotherapy Task F. The Canadian Association of Radiation Oncology scope of practice guidelines for lung, liver and spine stereotactic body radiotherapy. *Clin Oncol (R Coll Radiol)* 2012;24(9):629-639.
44. Bhattacharya IS, Hoskin PJ. Stereotactic body radiotherapy for spinal and bone metastases. *Clin Oncol (R Coll Radiol)* 2015;27(5):298-306.
45. Chang JH, Shin JH, Yamada YJ, Mesfin A, Fehlings MG, Rhines LD, Sahgal A. Stereotactic Body Radiotherapy for Spinal Metastases: What are the Risks and How Do We Minimize Them? *Spine (Phila Pa 1976)* 2016;41 Suppl 20:S238-S245.
46. Koswig S, Budach V. [Remineralization and pain relief in bone metastases after after different radiotherapy fractions (10 times 3 Gy vs. 1 time 8 Gy). A prospective study]. *Strahlenther Onkol* 1999;175(10):500-508.
47. Molina CA, Gokaslan ZL, Sciubba DM. A systematic review of the current role of minimally invasive spine surgery in the management of metastatic spine disease. *Int J Surg Oncol* 2011;2011:598148.
48. Rades D, Huttenlocher S, Dunst J, Bajrovic A, Karstens JH, Rudat V, Schild SE. Matched pair analysis comparing surgery followed by radiotherapy and radiotherapy alone for metastatic spinal cord compression. *J Clin Oncol* 2010;28(22):3597-3604.
49. Lopez-Olivo MA, Shah NA, Pratt G, Risser JM, Symanski E, Suarez-Almazor ME. Bisphosphonates in the treatment of patients with lung cancer and metastatic bone disease: a systematic review and meta-analysis. *Support Care Cancer* 2012;20(11):2985-2998.
50. Machado M, Cruz LS, Tannus G, Fonseca M. Efficacy of clodronate, pamidronate, and zoledronate in reducing morbidity and mortality in cancer patients with bone metastasis: a meta-analysis of randomized clinical trials. *Clin Ther* 2009;31(5):962-979.
51. Yuen KK, Shelley M, Sze WM, Wilt T, Mason MD. Bisphosphonates for advanced prostate cancer. *Cochrane Database Syst Rev* 2006(4):CD006250.
52. LeVasseur N, Clemons M, Hutton B, Shorr R, Jacobs C. Bone-targeted therapy use in patients with bone metastases from lung cancer: A systematic review of randomized controlled trials. *Cancer Treat Rev* 2016;50:183-193.
53. Wong MH, Stockler MR, Pavlakis N. Bisphosphonates and other bone agents for breast cancer. *Cochrane Database Syst Rev* 2012(2):CD003474.
54. Fizazi K, Carducci M, Smith M, Damiao R, Brown J, Karsh L, Milecki P, Shore N, Rader M, Wang H, Jiang Q, Tadros S, Dansey R, Goessl C. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. *Lancet* 2011;377(9768):813-822.
55. Fourney DR, Gokaslan ZL. Spinal instability and deformity due to neoplastic conditions. *Neurosurg Focus* 2003;14(1):e8.
56. White III AA, Panjabi MM. *Clinical Biomechanics of the spine*. Philadelphia: J.B. Lippincott Company, 1978.
57. Fisher CG, DiPaola CP, Ryken TC, Bilsky MH, Shaffrey CI, Berven SH, Harrop JS, Fehlings MG, Boriani S, Chou D, Schmidt MH, Polly DW, Biagini R, Burch S, Dekutoski MB, Ganju A, Gerszten PC, Gokaslan ZL, Groff MW, Liebsch NJ, Mendel E, Okuno SH, Patel S, Rhines LD, Rose PS, Sciubba DM, Sundaresan N, Tomita K, Varga PP, Vialle LR, Vrionis FD, Yamada Y, Fourney DR. A novel classification system for spinal instability in neoplastic disease: an evidence-based approach and expert consensus from the Spine Oncology Study Group. *Spine (Phila Pa 1976)* 2010;35(22):E1221-1229.
58. Weber MH, Burch S, Buckley J, Schmidt MH, Fehlings MG, Vrionis FD, Fisher CG. Instability and impending instability of the thoracolumbar spine in patients with spinal metastases: a systematic review. *Int J Oncol* 2011;38(1):5-12.

59. Cunha MV, Al-Omair A, Atenafu EG, Masucci GL, Letourneau D, Korol R, Yu E, Howard P, Lochray F, da Costa LB, Fehlings MG, Sahgal A. Vertebral compression fracture (VCF) after spine stereotactic body radiation therapy (SBRT): analysis of predictive factors. *Int J Radiat Oncol Biol Phys* 2012;84(3):e343-349.
60. Germano IM, Carai A, Pawha P, Blacksburn S, Lo YC, Green S. Clinical outcome of vertebral compression fracture after single fraction spine radiosurgery for spinal metastases. *Clin Exp Metastasis* 2016;33(2):143-149.
61. Sahgal A, Atenafu EG, Chao S, Al-Omair A, Boehling N, Balagamwala EH, Cunha M, Thibault I, Angelov L, Brown P, Suh J, Rhines LD, Fehlings MG, Chang E. Vertebral compression fracture after spine stereotactic body radiotherapy: a multi-institutional analysis with a focus on radiation dose and the spinal instability neoplastic score. *J Clin Oncol* 2013;31(27):3426-3431.
62. Sung SH, Chang UK. Evaluation of risk factors for vertebral compression fracture after stereotactic radiosurgery in spinal tumor patients. *Korean J Spine* 2014;11(3):103-108.
63. Denis F. The three column spine and its significance in the classification of acute thoracolumbar spinal injuries. *Spine (Phila Pa 1976)* 1983;8(8):817-831.
64. Denis F. Spinal instability as defined by the three-column spine concept in acute spinal trauma. *Clin Orthop Relat Res* 1984(189):65-76.
65. Van Kessel E, Verlaan JJ, Slooff WB, Wessels PH. [A score for rating instability in spinal metastases and the usefulness of conservative measures for instability]. *Ned Tijdschr Geneesk* 2013;157(24):A5331.
66. Taneichi H, Kaneda K, Takeda N, Abumi K, Satoh S. Risk factors and probability of vertebral body collapse in metastases of the thoracic and lumbar spine. *Spine (Phila Pa 1976)* 1997;22(3):239-245.
67. Campos M, Urrutia J, Zamora T, Roman J, Canessa V, Borghero Y, Palma A, Molina M. The Spine Instability Neoplastic Score: an independent reliability and reproducibility analysis. *Spine J* 2014;14(8):1466-1469.
68. Fisher CG, Schouten R, Versteeg AL, Boriani S, Varga PP, Rhines LD, Kawahara N, Fourny D, Weir L, Reynolds JJ, Sahgal A, Fehlings MG, Gokaslan ZL. Reliability of the Spinal Instability Neoplastic Score (SINS) among radiation oncologists: an assessment of instability secondary to spinal metastases. *Radiat Oncol* 2014;9:69.
69. Fourny DR, Frangou EM, Ryken TC, Dipaola CP, Shaffrey CI, Berven SH, Bilsky MH, Harrop JS, Fehlings MG, Boriani S, Chou D, Schmidt MH, Polly DW, Biagini R, Burch S, Dekutoski MB, Ganju A, Gerszten PC, Gokaslan ZL, Groff MW, Liebsch NJ, Mendel E, Okuno SH, Patel S, Rhines LD, Rose PS, Sciubba DM, Sundaresan N, Tomita K, Varga PP, Vialle LR, Vrionis FD, Yamada Y, Fisher CG. Spinal instability neoplastic score: an analysis of reliability and validity from the spine oncology study group. *J Clin Oncol* 2011;29(22):3072-3077.
70. Teixeira WG, Coutinho PR, Marchese LD, Narazaki DK, Cristante AF, Teixeira MJ, Barros Filho TE, Camargo OP. Interobserver agreement for the spine instability neoplastic score varies according to the experience of the evaluator. *Clinics (Sao Paulo)* 2013;68(2):213-218.
71. Arana E, Kovacs FM, Royuela A, Asenjo B, Perez-Ramirez U, Zamora J, Spanish Back Pain Research Network Task Force for the Improvement of Inter-Disciplinary Management of Spinal M. Spine Instability Neoplastic Score: agreement across different medical and surgical specialties. *Spine J* 2016;16(5):591-599.
72. Versteeg AL, Verlaan JJ, Sahgal A, Mendel E, Quraishi NA, Fourny DR, Fisher CG. The Spinal Instability Neoplastic Score: Impact on Oncologic Decision-Making. *Spine (Phila Pa 1976)* 2016;41 Suppl 20:S231-S237.
73. Aiba H, Kimura T, Yamagami T, Watanabe N, Sakurai H, Kimura H, Shimozaki S, Yamada S, Otsuka T. Prediction of skeletal-related events in patients with non-small cell lung cancer. *Support Care Cancer* 2016;24(8):3361-3367.
74. Lam TC, Uno H, Krishnan M, Lutz S, Groff M, Cheney M, Balboni T. Adverse Outcomes After Palliative Radiation Therapy for Uncomplicated Spine Metastases: Role of Spinal Instability and Single-Fraction Radiation Therapy. *Int J Radiat Oncol Biol Phys* 2015;93(2):373-381.
75. Lee SH, Tatsui CE, Ghia AJ, Amini B, Li J, Zavarella SM, Tannir NM, Brown PD, Rhines LD. Can the spinal instability neoplastic score prior to spinal radiosurgery predict compression fractures following

- stereotactic spinal radiosurgery for metastatic spinal tumor?: a post hoc analysis of prospective phase II single-institution trials. *J Neurooncol* 2016;126(3):509-517.
76. Versteeg AL, van der Velden JM, Verkooijen HM, van Vulpen M, Oner FC, Fisher CG, Verlaan JJ. The Effect of Introducing the Spinal Instability Neoplastic Score in Routine Clinical Practice for Patients With Spinal Metastases. *Oncologist* 2016;21(1):95-101.
 77. Chevalier Y, Charlebois M, Pahr D, Varga P, Heini P, Schneider E, Zysset P. A patient-specific finite element methodology to predict damage accumulation in vertebral bodies under axial compression, sagittal flexion and combined loads. *Comput Methods Biomech Biomed Engin* 2008;11(5):477-487.
 78. Chevalier Y, Pahr D, Charlebois M, Heini P, Schneider E, Zysset P. Cement distribution, volume, and compliance in vertebroplasty: some answers from an anatomy-based nonlinear finite element study. *Spine (Phila Pa 1976)* 2008;33(16):1722-1730.
 79. Chevalier Y, Pahr D, Zysset PK. The role of cortical shell and trabecular fabric in finite element analysis of the human vertebral body. *J Biomech Eng* 2009;131(11):111003.
 80. Matsuura Y, Giambini H, Ogawa Y, Fang Z, Thoreson AR, Yaszemski MJ, Lu L, An KN. Specimen-specific nonlinear finite element modeling to predict vertebrae fracture loads after vertebroplasty. *Spine (Phila Pa 1976)* 2014;39(22):E1291-1296.
 81. Pahr DH, Schwiedrzik J, Dall'Ara E, Zysset PK. Clinical versus pre-clinical FE models for vertebral body strength predictions. *J Mech Behav Biomed Mater* 2014;33:76-83.
 82. Liebschner MA, Kopperdahl DL, Rosenberg WS, Keaveny TM. Finite element modeling of the human thoracolumbar spine. *Spine (Phila Pa 1976)* 2003;28(6):559-565.
 83. Buckley JM, Loo K, Motherway J. Comparison of quantitative computed tomography-based measures in predicting vertebral compressive strength. *Bone* 2007;40(3):767-774.
 84. Crawford RP, Cann CE, Keaveny TM. Finite element models predict in vitro vertebral body compressive strength better than quantitative computed tomography. *Bone* 2003;33(4):744-750.
 85. Dall'Ara E, Schmidt R, Pahr D, Varga P, Chevalier Y, Patsch J, Kainberger F, Zysset P. A nonlinear finite element model validation study based on a novel experimental technique for inducing anterior wedge-shape fractures in human vertebral bodies in vitro. *J Biomech* 2010;43(12):2374-2380.
 86. Imai K. Analysis of vertebral bone strength, fracture pattern, and fracture location: a validation study using a computed tomography-based nonlinear finite element analysis. *Aging Dis* 2015;6(3):180-187.
 87. Imai K, Ohnishi I, Bessho M, Nakamura K. Nonlinear finite element model predicts vertebral bone strength and fracture site. *Spine (Phila Pa 1976)* 2006;31(16):1789-1794.
 88. Mirzaei M, Zeinali A, Razmjoo A, Nazemi M. On prediction of the strength levels and failure patterns of human vertebrae using quantitative computed tomography (QCT)-based finite element method. *J Biomech* 2009;42(11):1584-1591.
 89. Whyne CM, Hu SS, Klisch S, Lotz JC. Effect of the pedicle and posterior arch on vertebral body strength predictions in finite element modeling. *Spine (Phila Pa 1976)* 1998;23(8):899-907.
 90. Whyne CM, Hu SS, Lotz JC. Parametric finite element analysis of vertebral bodies affected by tumors. *J Biomech* 2001;34(10):1317-1324.
 91. Whyne CM, Hu SS, Lotz JC. Burst fracture in the metastatically involved spine: development, validation, and parametric analysis of a three-dimensional poroelastic finite-element model. *Spine (Phila Pa 1976)* 2003;28(7):652-660.
 92. Tschirhart CE, Finkelstein JA, Whyne CM. Biomechanics of vertebral level, geometry, and transcortical tumors in the metastatic spine. *J Biomech* 2007;40(1):46-54.
 93. Tschirhart CE, Nagpurkar A, Whyne CM. Effects of tumor location, shape and surface serration on burst fracture risk in the metastatic spine. *J Biomech* 2004;37(5):653-660.
 94. Sahli F, Cuellar J, Perez A, Fields AJ, Campos M, Ramos-Grez J. Structural parameters determining the strength of the porcine vertebral body affected by tumours. *Comput Methods Biomech Biomed Engin* 2015;18(8):890-899.
 95. Hojjat SP, Beek M, Akens MK, Whyne CM. Can micro-imaging based analysis methods quantify structural integrity of rat vertebrae with and without metastatic involvement? *J Biomech* 2012;45(14):2342-2348.

96. Choudhari C, Chan K, Akens MK, Whyne CM. muFE models can represent microdamaged regions of healthy and metastatically involved whole vertebrae identified through histology and contrast enhanced muCT imaging. *J Biomech* 2016;49(7):1103-1110.
97. Derikx LC, van Aken JB, Janssen D, Snyers A, van der Linden YM, Verdonchot N, Tanck E. The assessment of the risk of fracture in femora with metastatic lesions: comparing case-specific finite element analyses with predictions by clinical experts. *J Bone Joint Surg Br* 2012;94(8):1135-1142.
98. Tanck E, van Aken JB, van der Linden YM, Schreuder HW, Binkowski M, Huizenga H, Verdonchot N. Pathological fracture prediction in patients with metastatic lesions can be improved with quantitative computed tomography based computer models. *Bone* 2009;45(4):777-783.
99. Carpenter RD. Finite element analysis of the hip and spine based on quantitative computed tomography. *Curr Osteoporos Rep* 2013;11(2):156-162.
100. Tschirhart CE, Finkelstein JA, Whyne CM. Metastatic burst fracture risk assessment based on complex loading of the thoracic spine. *Ann Biomed Eng* 2006;34(3):494-505.
101. Braam P, Lambin P, Bussink J. Stereotactic versus conventional radiotherapy for pain reduction and quality of life in spinal metastases: study protocol for a randomized controlled trial. *Trials* 2016;17:61.



2

The Dutch national guideline on metastases and hematological malignancies localized within the spine; a multidisciplinary collaboration towards timely and proactive management

Karlijn H.J. Groenen, Yvette M. van der Linden, Thea Brouwer, Sander P.D. Dijkstra,
Alexander de Graeff, Paul R. Algra, Jos M.A. Kuijlen, Monique C. Minnema,
Claudia Nijboer, Davey L.H. Poelma, Christa Rolf, Tebbe Sluis, Michel A.M.B. Terheggen,
Alexandra C.M. van der Togt-van Leeuwen, Ronald H.M.A. Bartels, Walter Taal.

Cancer Treatment Reviews, under review

Introduction

Global cancer incidence rates are rising [1, 2], mainly due to the increasingly ageing population. These changes translate to a predicted 20 million new cancer cases worldwide by 2030, compared to an estimated 12.7 million cases in 2008 [3, 4]. Increased incidence together with longer survival result in more cancer patients being confronted with metastatic disease. The skeleton is often affected [5-8]. Bone metastases most frequently occur in the spinal column [9]; postmortem examination has demonstrated spinal metastases in approximately 70% of terminal cancer patients [10]. More than 50% of the spinal metastases are secondary tumors from breast, lung or prostate carcinomas [11]. Multiple myeloma and sometimes lymphomas may also affect the spinal column [12, 13].

Spinal metastases and localizations may lead to back pain, spinal instability, pathological fractures and deformity. Furthermore, epidural growth or vertebral collapse may be the cause of radiating neuropathic pain and neurological deficits due to compression of the spinal cord or nerve roots, all severely affecting the patient's quality of life. Consequently, instruction of patients, timely diagnosis, optimal local and/or systemic treatment, and adequate follow-up are of the utmost importance, so that progression of spinal metastases towards irreversible neurological damage may be prevented as much as possible.

However, in current clinical practice, care management of cancer patients with metastatic disease including spinal metastases is often reactive, responding to presenting clinical symptoms, rather than proactive, trying to prevent complications. Optimal diagnosis and management of patients with spinal metastases requires a multidisciplinary approach. This is, although difficult to arrange, in particular important in emergency situations such as metastatic epidural spinal cord compression (MESCC).

National and international multidisciplinary guidelines have the potential to strongly improve patient care. In the Netherlands, developing national guidelines has become routine practice since the late nineties, and numerous guidelines on both curative and palliative topics in cancer care have been developed, and are revised every five years [14, 15]. These guidelines provide evidence- and consensus-based recommendations and set requirements for standard of care on a national level. Guidelines are also being developed at an international level. For example, the American Society for Radiation Oncology (ASTRO) has developed a guideline for patients and clinicians regarding the use of radiotherapy in the treatment of bone metastases [16, 17].

In 2013, a national working group started to develop a new guideline on metastases and hematological malignancies localized within the spine. Four important principles were defined at the start:

1. The patients' perspective should be leading. Patients themselves should have an important role in the decision making processes (patient participation).

2. A proactive management should be pursued, resulting in rapid and adequate diagnosis and treatment, and preventing (progression of) pain and the occurrence of neurological deficits as much as possible.
3. Clear selection criteria for various treatments should be defined, taking into account spinal instability, spinal deformity, the patient's neurological prognosis, and life expectancy.
4. Organization, communication, and coordination of care should be optimized.

This paper describes the main results of the evidence-based approach to develop the Dutch National guideline on metastases and hematological malignancies localized within the spine. In addition, suggestions on implementation with practical considerations for institutes on how to organize care are discussed.

Methods

In 2013, the Dutch Neuro-Oncology Working Group (LWNO), supported by the Netherlands Comprehensive Cancer Organisation (IKNL), formed a multidisciplinary expert working group and tasked them with drafting a guideline on spinal metastases. Since symptoms, complications, and treatments of spinal localizations from hematological malignancies show great similarity with those of spinal metastases from solid tumors, they are included in this guideline. In addition, the guideline includes patients without as well as with MESCC. In the following, the term 'spinal metastases' will also include spinal localizations of hematologic malignancies, with and without MESCC, unless otherwise specified.

The members of the working group represented all regions of the Netherlands, both university and general hospitals, and all relevant medical disciplines. All working group members were representatives of their national scientific association, with a mandate for their input. The working group members had expertise in (alphabetical order) anesthesiology/pain medicine, epidemiology, general practice, guideline methodology, hematology, medical oncology, neurology, neurosurgery, nursing, orthopedics, radiology, radiotherapy, and rehabilitation. Most important, a patients' representative took an active seat in the working group to provide the patient perspective and was considered a full member. In total, 16 members were involved.

A survey was performed amongst both health care professionals and patients to make an inventory of the bottlenecks perceived in the various trajectories in patient care. A list of these bottlenecks was sent out to all related Dutch scientific and medical associations and patient organizations, asking them 1) to indicate whether they agreed with the bottlenecks; 2) to prioritize the bottlenecks and 3) to indicate whether they perceived additional bottlenecks. In addition to the bottleneck inventory, six patients were interviewed by telephone to gain insight in their perspective. These people were

recruited through the survey. Subsequently, fourteen clinical questions were formulated (Table 1).

Three clinical questions were addressed using an evidence-based approach (Table 1). For these questions, a systematic literature search was performed and/or supervised by a literature researcher/methodology expert. Work was carried out in accordance with the Guideline for Guidelines [18]. Question 2 (Table 1) was addressed in accordance with Evidence Based Guideline Development (EBRO), in which the level of evidence is assigned per study [19]. The intervention questions (questions 4 and 5, Table 1) were specified in accordance with Grading of Recommendations Assessment, Development and Evaluation, in which the level of evidence is assigned per outcome measure (GRADE) [20]. The remaining eleven questions were answered using a consensus-based approach. The literature search for these questions was carried out by the members of the working group themselves.

Each question was allocated to one of the working group members, based on his or her expertise, to act as chair. The analysis and writing processes per question were performed by two to four working group members. Subsequently, the whole working group plenary discussed and revised each chapter.

The patient advocate attended all guideline working group meetings, actively participated in the discussions and assessed the draft texts in order to optimize the patients' perspective in formulating the final text version. In addition, the working group verified whether the issues reported by the patients were sufficiently addressed in the guideline's conclusions and recommendations.

After approval by all workgroup members the draft guideline was presented to Dutch Neuro-Oncology Working Group (LWNO). The feedback by the LWNO members was processed by the guideline working group. The adapted draft guideline was then presented for comments to all scientific and professional associations and patient organizations that had been contacted within the framework of the bottleneck analysis, as well as to national and regional tumor working groups and the National Federation of Cancerpatientorganizations. We received 145 comments from 25 respondents. The comments received were evaluated and processed by the guideline working group. Eventually, the guideline was submitted to the relevant associations/authorities for authorization or approval. The final guideline became available online in August 2015.

With the help of the patient advocate and a 'www.kanker.nl' editor, patient information was written and is annexed to the guideline. This information is also available on www.kanker.nl [21], a national website especially designed for informing cancer patients.

This paper describes the key outcomes of the guideline. The complete guideline has been translated into English and is freely available on www.oncoline.nl/spinal-metastases.

Table 1 Clinical questions formulated based on the results of the bottleneck analysis.

	Clinical question	Consensus- (CB) or Evidence- Based (EB)
1	What criteria must a patient with spinal metastases meet to be eligible for surgery, followed by radiotherapy or radiotherapy alone?	CB
2	Based on a set of factors, how can survival with the best possible accuracy be assessed in patients with spinal metastases who are eligible for surgery and/or irradiation?	EB - EBRO*
3	How can the stability of metastatically affected vertebrae be determined in patients with spinal metastases in view of a possible stabilizing operation?	CB
4	Which technique (simple <i>versus</i> advanced technology) and radiotherapy dose results in the best possible outcome in patients with spinal metastases in terms of pain relief, mobility, morbidity, mortality, and costs?	EB - GRADE [‡]
5	Does surgery via an anterior approach compared to surgery via a posterior approach offer a better outcome in terms of mobility, morbidity, mortality, complications, and progression-free survival in patients with symptomatic spinal metastases? Does surgery by means of en bloc resection of the affected vertebra compared to removing the vertebra by the piece-meal method or through partial resection (debulking) offer a better outcome in terms of mobility, morbidity, mortality, complications, and progression-free survival in patients with symptomatic spinal metastases?	EB - GRADE
6	What is the effect of chemotherapy or hormonal therapy on neurological deficit, pain, and quality of life in patients with spinal metastases?	CB
7	Which patients with spinal metastases are eligible for percutaneous interventions, such as radiofrequency ablation (RFA) and vertebroplasty, with a view to reducing symptoms (e.g. pain), in terms of morbidity, complications and mortality?	CB
8	Does the care trajectory in patients with spinal metastases require the involvement of a pain team?	CB
9	How can questionnaires (pain score, neurological functional scales) be used systematically in patients with spinal metastases?	CB
10	How is the need detected for psychosocial assistance in patients with spinal metastases and how is this assistance offered?	CB
11	Is multidisciplinary consultation concerning patients with symptomatic spinal metastases always necessary and how will this be organized?	CB
12	Who follows up on the patient (and how)?	CB
13	How is an appropriate rehabilitation process established for patients with spinal metastases?	CB
14	Does the aftercare trajectory for patients with spinal metastases require the involvement of a rehabilitation specialist?	CB

* EBRO: Evidence Based Guideline Development; [‡] GRADE: Grading of Recommendations Assessment, Development and Evaluation.

Results

This chapter describes the main findings of the guideline based on the four principles mentioned above.

1. The patient perspective

During the bottlenecks analysis, patients identified the following points for improvement: having a say in the treatment, lack of available patient information on spinal metastases, lack of psycho-social care, the value of multidisciplinary consultation and the doctors' delay in case of symptoms possibly indicating the presence of spinal metastases. In addition, extensive patient information on spinal metastases has been developed and is annexed to the guideline.

2. Proactive care management

Preventing unnecessary delay

A randomized trial demonstrated that 3% of 342 patients with radiated painful spinal metastases eventually show signs of MESCC [22]. Although the risk of developing neurological deficits is relatively low, the consequences can be debilitating. Most patients who are still ambulant at the time of diagnosis remain their ambulatory status if treatment is started timely [23]. However, if treatment only begins when a patient is already bedridden due to severe neurological deficits, the chance of this patient regaining his/her walking ability is limited [23, 24]. Thus, to prevent progression towards a (complete) spinal cord injury or cauda equina syndrome as a result of symptomatic MESCC, it is important to diagnose as early as possible.

However, considerable patients' and also doctors' delays are unfortunately not uncommon [24, 25]. These delays are an important factor in neurological deficits and other adverse outcomes which possibly could have been prevented by a faster course of action [23, 26]. Therefore, an important goal of the guideline is to reduce these delays caused by either patients or physicians.

Raising awareness about the symptoms - The guideline describes symptoms that point at the presence of spinal metastases and symptoms indicating spinal instability and/or myelum or cauda compression. These so-called 'alarm symptoms' are described in Table 2. The working group considers it of major importance that patients with bone metastases and their general practitioners (GPs) are properly informed about the likelihood of spinal metastases, the alarm symptoms that (urgently) require contact, and who to contact in such case. To this end, the working group has developed a written patient information sheet on spinal metastases, including the alarm symptoms, which can be handed out to high-risk patients and their GPs, along with the local contact data. Of course, not only GPs but a broad range of health care professionals are confronted with patients with spinal metastases. To optimally collaborate and prevent delay, they should all be informed about the guideline and the accompanying patient sheet with alarm symptoms.

Table 2 Alarm symptoms that point at the presence of spinal metastases and indicating spinal instability and/or myelum or cauda compression.

Symptoms indicating the presence of spinal metastases in patients with cancer	Symptoms indicating spinal instability and/ or myelum or cauda compression
<ul style="list-style-type: none"> - New and/or increasing severe back or neck pain - Pain between the shoulder blades or just below - Back pain occurring when lying down (during sleep) and disappearing again when sitting up - Radiating pain in belly, chest, arms or legs 	<ul style="list-style-type: none"> - Decreased strength in the legs (including sometimes the arms) - Difficulty controlling the legs (including sometimes your arms) - A very wobbly gait - Numbness or tingling radiating down from chest, belly, groins and/or legs - Unable to walk and/or stand or legs give way

Clear deadlines for diagnosis and treatment - In addition to patient delay, there is also doctors' delay. This guideline contains recommendations and sets clear deadlines for imaging studies when spinal metastases are suspected (Figure 1). Spinal metastases cannot be excluded using conventional x-rays, CT scans and bone scintigraphy [25, 27]. Therefore, full spinal column Magnetic Resonance Imaging (MRI) is the test of first choice in patients with a clinical suspicion of spinal metastases, as MRI is superior to all other imaging modalities when it comes to demonstrating spinal metastases and compression of the myelum or cauda [28-33]. Both T1- and T2-weighted images are required to demonstrate spinal metastases and, in particular, spinal epidural metastases (SEM) and/or MESCC [28, 34, 35]. The deadline for MRI scanning depends on the nature of the patient's complaints (Table 3). An MRI should be made within two weeks in case the patient only has local back pain and within 12 hours if there is clinical suspicion of MESCC, in order to be able to start treatment promptly.

Table 3 Indications and deadlines for MRI scanning.

Symptom	Deadline for MRI scanning
- only local back pain	- within 2 weeks
- unilateral radicular pain	- within 1 week
- unilateral radicular deficit that develops in over 7 days and has a progressive nature	- Within 48 hours
- with unilateral radicular deficit that develops within 7 days and has a progressive nature	- Within 24 hours
- clinical suspicion of MESCC*	- As soon as possible, though at least within 12 hours

* In case of MESCC treatment should start well within 24 hours after MESCC is demonstrated.

In patients with suspected spinal metastases from unknown origin, there is a need to urgently obtain a histological diagnosis before treatment should start. The diagnostic timeframe in these patients depends on (the risk of) neurological deficits (see Figure 1).

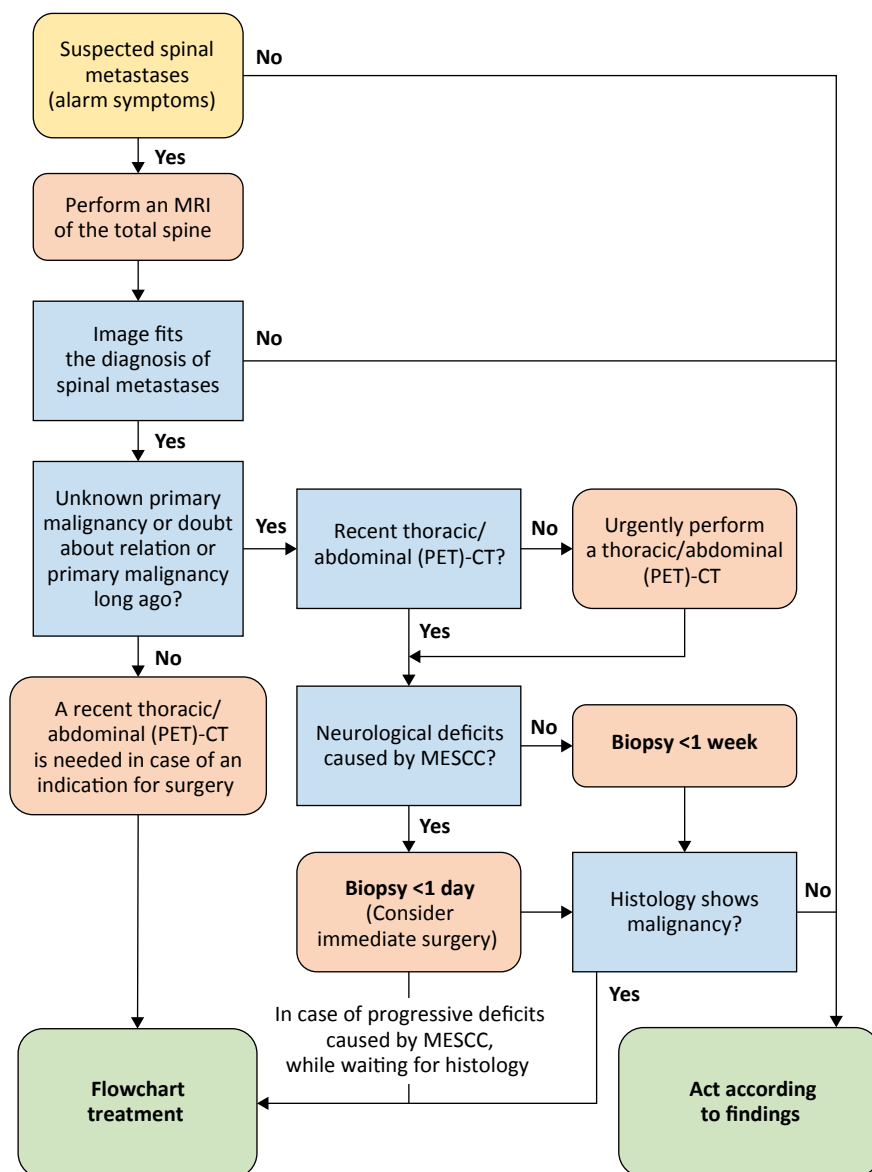


Figure 1 Flowchart on diagnostics in patients with suspected spinal metastases or spinal localization of hematological malignancies.

3. Treatment selection

The guideline extensively addresses a broad range of treatment modalities for patients with spinal metastases, among others radiotherapy, surgery, systemic treatments, and percutaneous interventions, with respect to their effectiveness on pain and neurological

problems. Based on the literature available, the working group has developed a flow diagram which describes the recommended selection of treatment based on estimated survival, estimated spinal (in)stability, and expected treatment outcome (Figure 2).

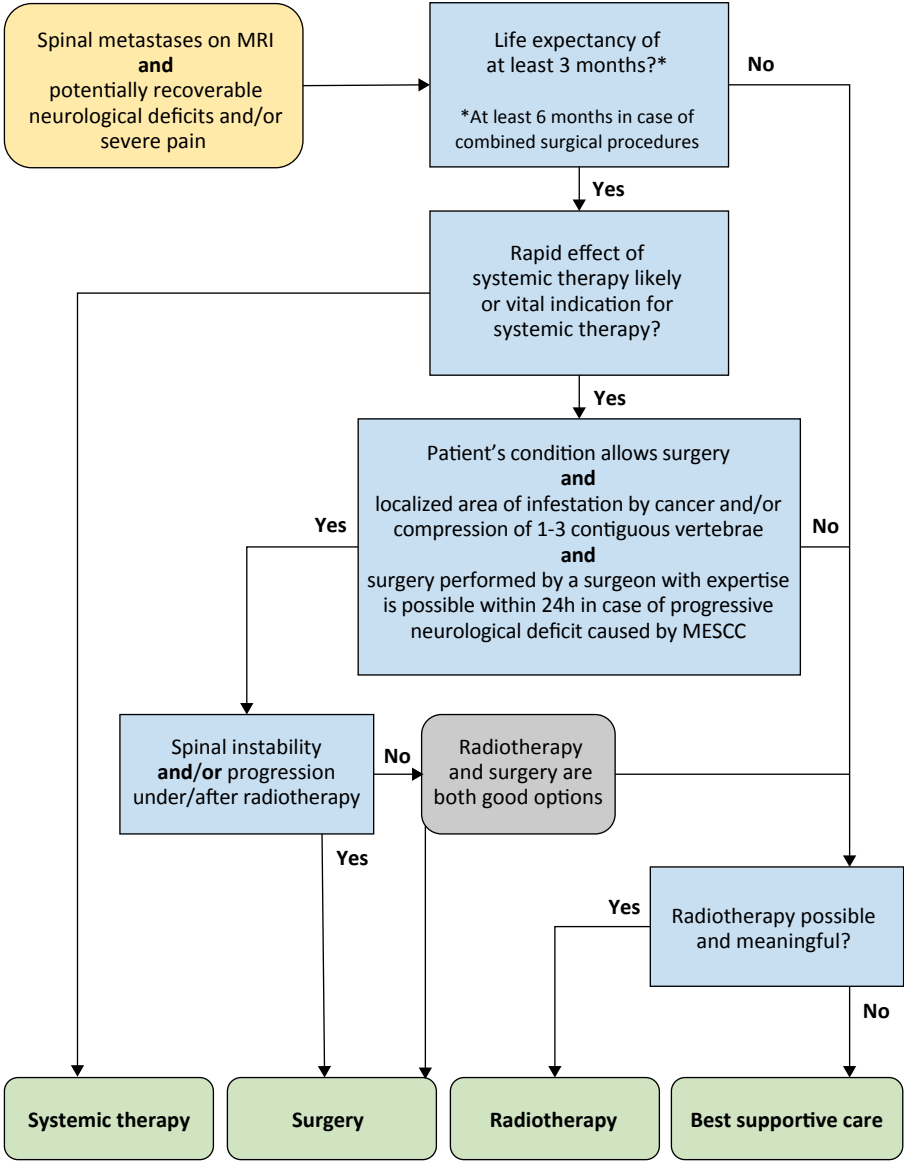


Figure 2 Flowchart on treatment selection in patients with symptomatic spinal metastases.

In general, radiotherapy is the treatment of first choice in patients with symptomatic (with pain and/or neurological deficit) spinal metastases, provided that an adequate

radiotherapy dose can be given. For surgery, a life expectancy of at least three months, a good clinical situation of the patient, and a limited area of damage and/or obstruction are required. Surgery is the preferred treatment in case of (1) spinal instability; and/or (2) recurrence or progression of pain and/or neurological deficits following radiotherapy and without options for repeat radiotherapy; and/or (3) neurological deterioration under radiotherapy and corticosteroids. In case of MESCC-induced neurologic deficits surgery and radiotherapy are equivalent options. A treatment choice should be made on the basis of a (ad hoc) multidisciplinary discussion (see 4. Organisation of care – Multidisciplinary cooperation), and patient preference following the concept of shared decision making. Detailed information on radiotherapy type and dose and type of surgery is described in the guideline.

Systemic treatment is given as primary treatment if there is a high chance of response (e.g. in multiple myeloma and some types of malignant lymphoma).

Assessing survival

An accurate assessment of life expectancy is required to prevent both overtreatment (extensive surgery in patients with short-term survival) and undertreatment (forgoing treatment in patients with long-term survival). However, two systematic reviews showed that assessment of life expectancy based on clinical experience by physicians is inaccurate [36, 37].

The literature describes several prognostic models that can be used as a tool for predicting survival on the basis of patient-specific risk factors. Four externally validated models with at least the risk factors primary tumor and performance status were identified: Tokuhashi [38], Van der Linden [22], Bartels [39] and Bollen [11]. Details of these prognostic models can be found in Table 4. The accuracy of the Tokuhashi model varies greatly [40-44]. The other models have shown to permit a reliable assessment of the survival of patients with symptomatic spinal metastases, with no model being superior to the others [11, 45, 46].

Assessing spinal (in)stability

The Spinal Instability Neoplastic Score (SINS) is the first attempt to register mechanical instability due to metastatic disease [47]. The SINS has been developed to help physicians gain insight into the degree of instability using six radiological and clinical components. Although the SINS is reproducible and yields a good inter- and intra-observer agreement [48, 49], to date no prospective study has been published to validate the SINS's predictive power to differentiate between lesions at risk and not at risk of progressive debilitating instability. Therefore, the use of SINS as an absolute tool to differentiate between stable and unstable, leading to a decision to perform surgery or not, is not advised in this guideline. For now, spinal (in)stability is judged clinically and radiologically. It is recommended to discuss all patients with a (potentially) unstable spinal column with the spinal surgeon.

Table 4 Details of prognostic models on survival.

	Tokuhashi	Van der Linden	Bartels	Bollen
Original population (n=)	246	342	219	1043
C score*	0.640	0.664	0.719	0.710
Risk factor				
- Primary tumor	X	X	X	X
- Performance status	X	X	X	X
- Visceral metastases	X	X		X
- Bone metastases	X			
- Number of spinal metastases	X			
- Neurological functioning	X			
- Location of spinal metastases			X	
- Gender			X	
- Curative tumor treatment			X	

*The C score contains an estimation of the probability of similarity between the predicted and observed survival. The C score may vary from 0.50 (no predictive value) to 1.0 (complete similarity between predicted and actual survival).

4. Organization of care

Multidisciplinary cooperation

Determining the best treatment for a patient with spinal metastases is a complex process and requires a multidisciplinary approach. Multidisciplinary consultation (MC) meetings are mentioned increasingly in guidelines and indicator sets [15, 50, 51]. The study by Fitzpatrick et al. [50], demonstrated that the number of incorrect referrals of patients for epidural spinal metastasis surgery reduces if prior virtual consultation (by email, telephone and imaging via the online PACS system) with the spinal surgeon takes place. Although there is no other evidence to support the effectiveness of an MC meeting for patients with spinal metastases, the guideline committee believes a MC meeting is essential for optimal proactive management for patients with spinal metastases. All patients with symptomatic spinal metastases should be discussed in an MC meeting, with a representative of the original treating specialty (e.g. medical oncologist, hematologist), a radiation oncologist, a radiologist, a neurologist or neuro-oncologist (in case of neurological deficits) and (in case of a potential surgery indication for surgery) the spine surgeon being present. This consultation can take place during a weekly structured MC meeting, but in case of urgency, e.g. progressive neurological deficit, an ad hoc consultation with at least the responsible physician, the radiation oncologist, and spine surgeon is required.

Optimal palliative care

With the exception of malignancies that can be cured using chemotherapy (e.g. non-Hodgkin lymphomas), most patients with spinal metastases are in the palliative phase of their disease. According to the definition by the World Health Organization, palliative care is an approach that improves the quality of life of patients and their families facing

the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual [52]. This aim of care requires a substantial change in the way the patient and his or her relatives are approached. The current guideline emphasizes that attention should be paid to all aspects of care: physical, psychological, social, as well as spiritual [53].

In addition, it should be investigated, taking into account the patient's wishes and life expectancy, whether appropriate actions can be taken to achieve optimal functioning. Therefore, the possibilities to (re)gain function by means of e.g. a rehabilitation trajectory, physical therapy, or occupational therapy should be explored.

Coordination of care and communication

Coordination of care and optimal communication between all health care professionals involved are essential for the best possible care for patients with spinal metastases. Therefore, it is of major importance to designate the responsible physician, i.e. the clinician who is the first point of contact for the patient and other care providers and who also controls and coordinates the care provided to the patient. In the phase of disease-oriented palliation this will mostly be a hospital medical specialist, e.g. a medical oncologist or hematologist. During the phase of symptom-oriented palliation, care shifts increasingly to the GP or the geriatric specialist. The principal care provider will ensure a proper, preferably verbal as well as written, transfer of care. Such a transfer of care may concern a transfer within the hospital, as well as a transfer from the hospital specialist to the GP. The patient should at any time be well aware of who his or her responsible physician is.

Ideally, the patient's GP should play a central role and, therefore, be actively involved as early as possible during the trajectory. It is desirable to make sure the GP is well-informed of the situation at all times: which vertebrae are affected (results of most recent diagnostic imaging), what symptoms can be expected, what to do in case of such symptoms, and the possible options for treatment. Consultation of a palliative care team should be available at all times for the GP or specialist in case of complicated situations.

Discussion

The Dutch national guideline on metastases from solid tumors and hematological malignancies localized within the spine not only focuses on treatment choices, but also addresses important topics such as proactive care guided towards prevention of complications, proper patient selection using predictive models, multidisciplinary collaboration and optimal organization of care, all based on the needs and wishes of patients.

Clinical guidelines aim to standardize and improve patient care by providing recommendations about appropriate care in specific clinical circumstances, by integrating clinical expertise, the best evidence available, and patient values. However, a discrepancy between best practice, as determined by scientific evidence, and actual clinical care often exists. In general, about 30-40% of patients do not receive care according to present scientific evidence, and about 20-25% of care provided is unnecessary or even potentially harmful to patients [54].

Since information on potential barriers and incentives for changes can be used to tailor implementation strategies, understanding the factors that facilitate or hinder change in clinical practice could aid in bridging the gap between scientific evidence and patient care [55]. Therefore, below some additional comments are made on the issues raised in the guideline.

A proactive care management is pursued by reducing both doctors' and patients' delay in diagnosis and treatment of spinal metastases as much as possible. The guideline emphasizes that this delay can be handled on two levels: by increasing awareness of the alarm symptoms indicating the presence and complications of spinal metastases, and by setting clear deadlines for appropriate and timely diagnostics and treatment. This aids in preventing - as much as possible - debilitating clinical symptoms such as progressive pain, spinal instability, and/or neurological deficits.

The education of patients and clinicians, both hospital specialists and GPs, should focus on recognizing the alarm symptoms. Routing of information on the presence and complications of spinal metastases is challenging, as patients with cancer are seen and treated in numerous institutes and by various clinicians, including GPs. Therefore, it requires per institution and between the clinicians interdisciplinary communication and clear agreements on who furnishes the patient information including the alarm symptoms to the patients. These working arrangements together with the patient information sheet should be easily accessible through a content management system. Moreover, adopting information on the alarm symptoms on websites for cancer patients and implementing the information in patient information brochures of the involved medical specialties might aid in educating patients. To this end, the patient information has been made available online on a national website especially designed for cancer patients (www.kanker.nl) as well as on a website comprising a database with oncology related guidelines [15]. Finally, the responsible physician is accountable for ensuring that patient is informed adequately.

With regard to timely diagnostics and treatment, easy access to diagnostic imaging and treatment, i.e. radiotherapy and spinal surgery facilities, should be available. The guideline sets clear and relatively tight deadlines for diagnostics, depending on the severity of the patient's symptoms. Therefore, it is important that institutions maintain a policy which enables easy access to diagnostic imaging.

Treatment selection criteria in the guideline are based on estimated survival, degree of spinal instability and expected treatment outcome. For estimating survival, the

prognostics models published by Van der Linden et al. [22], Bartels et al. [39], or Bollen et al. [11] are advised by the guideline. However, it must be noted that although these models show comparable results, the patient populations with spinal metastases on which the models are based vary greatly. For instance, the Van der Linden model contains patients with only pain, about 50% of the Bollen patients have neurological signs, and in the Bartels population 84% has neurological complaints. In addition, these models have been developed and, partly, validated in Dutch patients and are, therefore, considered to be valid for the Dutch patient populations. The Van der Linden model has already been successfully validated in the Canadian population [46] and the Bartels model has also been geographically and prospectively validated [45, 56]. Nevertheless, for international use however these models should be further validated.

In addition, these models were based on current clinical practice. However, new treatment options are being developed, expected to increase the survival in patients with spinal metastases. Also, new insights are gained in e.g. the effect of tumor profile or mutation status on survival [57, 58]. Hence, currently existing prognostic models should continuously be updated.

Despite additional literature concerning the SINS score has become available since the publication of the guideline [59-62], validation of the SINS's predictive power to discriminate between lesions at risk at not at risk of progressive debilitating instability in a prospective setting is still lacking. In addition, more recent studies have reported contradicting findings on the inter- and intra-rater reliability [49, 61, 63, 64]. Therefore, the guideline advises against the use of the SINS as predictor for progressive spinal instability. It could, however, be useful as a tool for streamlining communication between physicians of different medical specialties and facilitating the decision making concerning surgical consultation.

With regard to organization of care, the guideline recommends discussing all patients with symptomatic spinal metastases in a multidisciplinary meeting. In several academic and other hospitals pilots with weekly MC meetings are taking place. In more acute situations (e.g. MESCC, severe pain, and/or spinal instability), there usually is no time to wait for the weekly multidisciplinary meeting as treatment should be initiated quickly. In such case an ad hoc consultation should be arranged. Ideally the physicians involved will meet in person, but a telephone meeting or more modern techniques, e.g. Skype for Business and digital transfer of PACS images, increasingly offer solutions, also if physicians are working in different institutes or on different locations.

In addition, the guideline advises that it should be clear to the patient and all care givers involved who the responsible physician is. It is recommended to register this in the patient's file and to formalize the responsible physician's tasks and responsibilities.

Moreover, we are well aware of the fact that the current guideline prescribes a prominent role for the GP. In the Netherlands, all citizens are registered with a GP (also named family doctor or family physician) offering primary care, which is reimbursed by the (mandatory) health insurance. As a result of this easily accessible primary care, the

Dutch GP has a good overview of the health status of his or her patient, provides a major part of the palliative care, and may serve as responsible physician. In other countries the role of the GP may be different.

Conclusion

This national multidisciplinary guideline aims to improve the quality of care for patients with metastases from solid tumors and hematological malignancies localized within the spine and, as a consequence, their quality of life. Four important principles are defined: (1) The patients' perspective is leading; (2) Proactive management is directed at preventing complications; (3) Clear treatment selection criteria are defined; and (4) Organization, communication, and coordination of care is optimized. The guideline explicitly pursues proactive, multidisciplinary patient care and gives recommendations about diagnostics, treatment modalities, patient selection, follow-up, organization of care, and palliative care. Finally, practical considerations regarding implementation of the guideline are discussed.

Acknowledgments

In addition to the authors of this article, many thanks to the advisors of the Working Group for their contribution to the development of "The Dutch national guideline on metastases and hematological malignancies localized within the spine; a multidisciplinary collaboration towards timely and proactive management": W.C. Peul, MD, PhD (Department of Neurosurgery, Leiden University Medical Center, Leiden, The Netherlands), W.C.H. Jacobs, PhD (Department of Neurosurgery, Leiden University Medical Center, Leiden, The Netherlands), L. Bollen, MD (Department of Orthopaedic Surgery, Leiden University Medical Center, Leiden, The Netherlands), and O. van der Hel, PhD (Netherlands Comprehensive Cancer Organisation (IKNL), Rotterdam, The Netherlands). We further acknowledge A. van der Mei, MSc (Netherlands Comprehensive Cancer Organisation (IKNL), Groningen, The Netherlands) and R. de Peuter, MSc (Netherlands Comprehensive Cancer Organisation (IKNL), Utrecht, The Netherlands) for the secretarial support and E.W. de Vries for grammar and spelling checking the English version of the guideline.

References

1. Signaleringscommissie Kanker van KWF Kankerbestrijding. Kanker in Nederland tot 2020. Trends en prognoses. Amsterdam: KWF Kankerbestrijding, 2011.
2. Smith BD, Smith GL, Hurria A, Hortobagyi GN, Buchholz TA. Future of cancer incidence in the United States: burdens upon an aging, changing nation. *J Clin Oncol* 2009;27(17):2758-2765.
3. Bray F, Jemal A, Grey N, Ferlay J, Forman D. Global cancer transitions according to the Human Development Index (2008-2030): a population-based study. *Lancet Oncol* 2012;13(8):790-801.
4. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer* 2010;127(12):2893-2917.
5. Belliveau RE, Spencer RP. Incidence and sites of bone lesions detected by 99mTc-polyphosphate scans in patients with tumors. *Cancer* 1975;36(2):359-363.
6. Coleman RE. Skeletal complications of malignancy. *Cancer* 1997;80(8 Suppl):1588-1594.
7. Gralow JR, Biermann JS, Farooki A, Fornier MN, Gagel RF, Kumar R, Litsas G, McKay R, Podoloff DA, Srinivas S, Van Poznak CH. NCCN Task Force Report: Bone Health In Cancer Care. *J Natl Compr Canc Netw* 2013;11 Suppl 3:S1-50; quiz S51.
8. Tofe AJ, Francis MD, Harvey WJ. Correlation of neoplasms with incidence and localization of skeletal metastases: An analysis of 1,355 diphosphonate bone scans. *J Nucl Med* 1975;16(11):986-989.
9. Kakhki VR, Anvari K, Sadeghi R, Mahmoudian AS, Torabian-Kakhki M. Pattern and distribution of bone metastases in common malignant tumors. *Nucl Med Rev Cent East Eur* 2013;16(2):66-69.
10. Perrin RG, Laxton AW. Metastatic spine disease: epidemiology, pathophysiology, and evaluation of patients. *Neurosurg Clin N Am* 2004;15(4):365-373.
11. Bollen L, van der Linden YM, Pondaag W, Fiocco M, Pattynama BP, Marijnen CA, Nelissen RG, Peul WC, Dijkstra PD. Prognostic factors associated with survival in patients with symptomatic spinal bone metastases: a retrospective cohort study of 1,043 patients. *Neuro Oncol* 2014;16(7):991-998.
12. Bach F, Larsen BH, Rohde K, Borgesen SE, Gjerris F, Boge-Rasmussen T, Agerlin N, Rasmusson B, Stjernholm P, Sorensen PS. Metastatic spinal cord compression. Occurrence, symptoms, clinical presentations and prognosis in 398 patients with spinal cord compression. *Acta Neurochir (Wien)* 1990;107(1-2):37-43.
13. Sorensen S, Borgesen SE, Rohde K, Rasmusson B, Bach F, Boge-Rasmussen T, Stjernholm P, Larsen BH, Agerlin N, Gjerris F, et al. Metastatic epidural spinal cord compression. Results of treatment and survival. *Cancer* 1990;65(7):1502-1508.
14. Comprehensive Cancer Centre the Netherlands. Palliative Guidelines Palliative Care. Last accessed 2017. Available from: <http://www.palliative.nl/>.
15. Comprehensive Cancer Centre the Netherlands. Oncoline Cancer Clinical Practice Guidelines. Last accessed 2017. Available from: <http://www.oncoline.nl/index.php?language=en>.
16. Lutz S, Balboni T, Jones J, Lo S, Petit J, Rich SE, Wong R, Hahn C. Palliative radiation therapy for bone metastases: Update of an ASTRO Evidence-Based Guideline. *Pract Radiat Oncol* 2017;7(1):4-12.
17. Lutz S, Berk L, Chang E, Chow E, Hahn C, Hoskin P, Howell D, Konski A, Kachnic L, Lo S, Sahgal A, Silverman L, von Gunten C, Mendel E, Vassil A, Bruner DW, Hartsell W, American Society for Radiation O. Palliative radiotherapy for bone metastases: an ASTRO evidence-based guideline. *Int J Radiat Oncol Biol Phys* 2011;79(4):965-976.
18. Regieraad Kwaliteit van Zorg. Richtlijn voor Richtlijnen. Last accessed 2017. Available from: http://www.ha-ring.nl/download/literatuur/Richtlijn_voor_Richtlijnen_derde_herziene_versie.pdf.
19. Burgers JS, van Everdingen JJ. [Evidence-based guideline development in the Netherlands: the EBRO platform]. *Ned Tijdschr Geneesk* 2004;148(42):2057-2059.
20. GRADE working group. GRADE. Last accessed 2017. Available from: www.gradeworkinggroup.org/.
21. Stichting Kanker.nl. Kanker.nl. Last accessed 2017. Available from: <https://www.kanker.nl/>.
22. Van der Linden YM, Dijkstra SP, Vonk EJ, Marijnen CA, Leer JW, Dutch Bone Metastasis Study G. Prediction of survival in patients with metastases in the spinal column: results based on a randomized trial of radiotherapy. *Cancer* 2005;103(2):320-328.
23. Rades D, Douglas S, Huttenlocher S, Rudat V, Veninga T, Stalpers LJ, Basic H, Karstens JH, Hoskin PJ, Adamietz IA, Schild SE. Validation of a score predicting post-treatment ambulatory status after radiotherapy for metastatic spinal cord compression. *Int J Radiat Oncol Biol Phys* 2011;79(5):1503-1506.

24. Husband DJ. Malignant spinal cord compression: prospective study of delays in referral and treatment. *BMJ* 1998;317(7150):18-21.
25. Kienstra GE, Terwee CB, Dekker FW, Canta LR, Borstlap AC, Tijssen CC, Bosch DA, Tijssen JG. Prediction of spinal epidural metastases. *Arch Neurol* 2000;57(5):690-695.
26. Helweg-Larsen S, Sorensen PS, Kreiner S. Prognostic factors in metastatic spinal cord compression: a prospective study using multivariate analysis of variables influencing survival and gait function in 153 patients. *Int J Radiat Oncol Biol Phys* 2000;46(5):1163-1169.
27. Avrahami E, Tadmor R, Dally O, Hadar H. Early MR demonstration of spinal metastases in patients with normal radiographs and CT and radionuclide bone scans. *J Comput Assist Tomogr* 1989;13(4):598-602.
28. Algra PR, Bloem JL, Tissing H, Falke TH, Arndt JW, Verboom LJ. Detection of vertebral metastases: comparison between MR imaging and bone scintigraphy. *Radiographics* 1991;11(2):219-232.
29. Buhmann Kirchhoff S, Becker C, Duerr HR, Reiser M, Baur-Melnyk A. Detection of osseous metastases of the spine: comparison of high resolution multi-detector-CT with MRI. *Eur J Radiol* 2009;69(3):567-573.
30. Daffner RH, Lupetin AR, Dash N, Deeb ZL, Sefczek RJ, Schapiro RL. MRI in the detection of malignant infiltration of bone marrow. *AJR Am J Roentgenol* 1986;146(2):353-358.
31. Steinborn MM, Heuck AF, Tiling R, Bruegel M, Gauger L, Reiser MF. Whole-body bone marrow MRI in patients with metastatic disease to the skeletal system. *J Comput Assist Tomogr* 1999;23(1):123-129.
32. Steiner RM, Mitchell DG, Rao VM, Schweitzer ME. Magnetic resonance imaging of diffuse bone marrow disease. *Radiol Clin North Am* 1993;31(2):383-409.
33. Vanel D, Bittoun J, Tardivon A. MRI of bone metastases. *Eur Radiol* 1998;8(8):1345-1351.
34. Bilsky MH, Laufer I, Fournay DR, Groff M, Schmidt MH, Varga PP, Vrionis FD, Yamada Y, Gerszten PC, Kuklo TR. Reliability analysis of the epidural spinal cord compression scale. *J Neurosurg Spine* 2010;13(3):324-328.
35. Kim JK, Learch TJ, Colletti PM, Lee JW, Tran SD, Terk MR. Diagnosis of vertebral metastasis, epidural metastasis, and malignant spinal cord compression: are T(1)-weighted sagittal images sufficient? *Magn Reson Imaging* 2000;18(7):819-824.
36. Chow E, Harth T, Hruby G, Finkelstein J, Wu J, Danjoux C. How accurate are physicians' clinical predictions of survival and the available prognostic tools in estimating survival times in terminally ill cancer patients? A systematic review. *Clin Oncol (R Coll Radiol)* 2001;13(3):209-218.
37. Glare P, Virik K, Jones M, Hudson M, Eychmuller S, Simes J, Christakis N. A systematic review of physicians' survival predictions in terminally ill cancer patients. *BMJ* 2003;327(7408):195-198.
38. Tokuhashi Y, Matsuzaki H, Oda H, Oshima M, Ryu J. A revised scoring system for preoperative evaluation of metastatic spine tumor prognosis. *Spine (Phila Pa 1976)* 2005;30(19):2186-2191.
39. Bartels RH, Feuth T, van der Maazen R, Verbeek AL, Kappelle AC, Andre Grotenhuis J, Leer JW. Development of a model with which to predict the life expectancy of patients with spinal epidural metastasis. *Cancer* 2007;110(9):2042-2049.
40. Gakhar H, Swamy GN, Bommireddy R, Calthorpe D, Klezl Z. A study investigating the validity of modified Tokuhashi score to decide surgical intervention in patients with metastatic spinal cancer. *Eur Spine J* 2013;22(3):565-568.
41. Hernandez-Fernandez A, Velez R, Lersundi-Artamendi A, Pellise F. External validity of the Tokuhashi score in patients with vertebral metastasis. *J Cancer Res Clin Oncol* 2012;138(9):1493-1500.
42. Tabouret E, Cauvin C, Fuentes S, Esterni B, Adetchessi T, Salem N, Madroszyk A, Goncalves A, Casalonga F, Gravis G. Reassessment of scoring systems and prognostic factors for metastatic spinal cord compression. *Spine J* 2015;15(5):944-950.
43. Wang M, Bunker CE, Li H, Wu C, Hoy K, Niedermann B, Helmig P, Wang Y, Jensen AB, Schattiger K, Hansen ES. Predictive value of Tokuhashi scoring systems in spinal metastases, focusing on various primary tumor groups: evaluation of 448 patients in the Aarhus spinal metastases database. *Spine (Phila Pa 1976)* 2012;37(7):573-582.
44. Yamashita T, Siemionow KB, Mroz TE, Podichetty V, Lieberman IH. A prospective analysis of prognostic factors in patients with spinal metastases: use of the revised Tokuhashi score. *Spine (Phila Pa 1976)* 2011;36(11):910-917.
45. Bartels RH, Feuth T, Rades D, Hedlund R, Villas C, van der Linden Y, Borm W, Kappelle A, van der Maazen RW, Grotenhuis JA, Verbeek AL. External validation of a model to predict the survival of patients presenting with a spinal epidural metastasis. *Cancer Metastasis Rev* 2011;30(2):153-159.
46. Chow E, Harris K, Fung K. Successful validation of a survival prediction model in patients with metastases in the spinal column. *Int J Radiat Oncol Biol Phys* 2006;65(5):1522-1527.

47. Fisher CG, DiPaola CP, Ryken TC, Bilsky MH, Shaffrey CI, Berven SH, Harrop JS, Fehlings MG, Boriani S, Chou D, Schmidt MH, Polly DW, Biagini R, Burch S, Dekutoski MB, Ganju A, Gerszten PC, Gokaslan ZL, Groff MW, Liebsch NJ, Mendel E, Okuno SH, Patel S, Rhines LD, Rose PS, Sciubba DM, Sundaresan N, Tomita K, Varga PP, Vialle LR, Vrionis FD, Yamada Y, Fournery DR. A novel classification system for spinal instability in neoplastic disease: an evidence-based approach and expert consensus from the Spine Oncology Study Group. *Spine (Phila Pa 1976)* 2010;35(22):E1221-1229.
48. Fisher CG, Schouten R, Versteeg AL, Boriani S, Varga PP, Rhines LD, Kawahara N, Fournery D, Weir L, Reynolds JJ, Sahgal A, Fehlings MG, Gokaslan ZL. Reliability of the Spinal Instability Neoplastic Score (SINS) among radiation oncologists: an assessment of instability secondary to spinal metastases. *Radiat Oncol* 2014;9:69.
49. Fournery DR, Frangou EM, Ryken TC, DiPaola CP, Shaffrey CI, Berven SH, Bilsky MH, Harrop JS, Fehlings MG, Boriani S, Chou D, Schmidt MH, Polly DW, Biagini R, Burch S, Dekutoski MB, Ganju A, Gerszten PC, Gokaslan ZL, Groff MW, Liebsch NJ, Mendel E, Okuno SH, Patel S, Rhines LD, Rose PS, Sciubba DM, Sundaresan N, Tomita K, Varga PP, Vialle LR, Vrionis FD, Yamada Y, Fisher CG. Spinal instability neoplastic score: an analysis of reliability and validity from the spine oncology study group. *J Clin Oncol* 2011;29(22):3072-3077.
50. Fitzpatrick D, Grabarz D, Wang L, Bezjak A, Fehlings MG, Fosker C, Rampersaud R, Wong RKS. How Effective Is a Virtual Consultation Process in Facilitating Multidisciplinary Decision-Making for Malignant Epidural Spinal Cord Compression? *Int J Radiat Oncol* 2012;84(2):E167-E172.
51. Ottevanger N, Hilbink M, Weenk M, Janssen R, Vrijmoeth T, de Vries A, Hermens R. Oncologic multidisciplinary team meetings: evaluation of quality criteria. *J Eval Clin Pract* 2013;19(6):1035-1043.
52. World Health Organization. WHO Definition of palliative care. Last accessed 2017. Available from: <http://www.who.int/cancer/palliative/definition/en/>.
53. Comprehensive Cancer Centre the Netherlands. Palliative Guidelines Palliative Care - Algemene principes van palliatieve zorg. Last accessed 2017. Available from: <http://www.palliative.nl/algemene-principes-van-palliatieve-zorg>.
54. Grol R, Grimshaw J. From best evidence to best practice: effective implementation of change in patients' care. *Lancet* 2003;362(9391):1225-1230.
55. Grol R, Wensing M. What drives change? Barriers to and incentives for achieving evidence-based practice. *Med J Aust* 2004;180(6 Suppl):S57-60.
56. Bartels RH, de Ruiter G, Feuth T, Arts MP. Prediction of life expectancy in patients with spinal epidural metastasis. *Neuro Oncol* 2016;18(1):114-118.
57. Bollen L, Wibmer C, Wang M, van der Linden YM, Leithner A, Bunger CE, Jensen AB, Fiocco M, Bratschitsch G, Pondaag W, Bovee JV, Dijkstra PD. Molecular phenotype is associated with survival in breast cancer patients with spinal bone metastases. *Clin Exp Metastasis* 2015;32(1):1-5.
58. Willeumier JJ, van der Hoeven NM, Bollen L, Willems LN, Fiocco M, van der Linden YM, Dijkstra PD. Epidermal growth factor receptor mutations should be considered as a prognostic factor for survival of patients with pathological fractures or painful bone metastases from non-small cell lung cancer. *Bone Joint J* 2017;99-B(4):516-521.
59. Germano IM, Carai A, Pawha P, Blackburn S, Lo YC, Green S. Clinical outcome of vertebral compression fracture after single fraction spine radiosurgery for spinal metastases. *Clin Exp Metastasis* 2016;33(2):143-149.
60. Versteeg AL, Verlaan JJ, Sahgal A, Mendel E, Quraishi NA, Fournery DR, Fisher CG. The Spinal Instability Neoplastic Score: Impact on Oncologic Decision-Making. *Spine (Phila Pa 1976)* 2016;41 Suppl 20:S231-S237.
61. Bollen L, Groenen K, Pondaag W, van Rijswijk CSP, Fiocco M, Van der Linden YM, Dijkstra SPD. Clinical Evaluation of the Spinal Instability Neoplastic Score in Patients Treated With Radiotherapy for Symptomatic Spinal Bone Metastases. *Spine (Phila Pa 1976)* 2017;42(16):E956-E962.
62. Lam TC, Uno H, Krishnan M, Lutz S, Groff M, Cheney M, Balboni T. Adverse Outcomes After Palliative Radiation Therapy for Uncomplicated Spine Metastases: Role of Spinal Instability and Single-Fraction Radiation Therapy. *Int J Radiat Oncol Biol Phys* 2015;93(2):373-381.
63. Campos M, Urrutia J, Zamora T, Roman J, Canessa V, Borghero Y, Palma A, Molina M. The Spine Instability Neoplastic Score: an independent reliability and reproducibility analysis. *Spine J* 2014;14(8):1466-1469.
64. Teixeira WG, Coutinho PR, Marchese LD, Narazaki DK, Cristante AF, Teixeira MJ, Barros Filho TE, Camargo OP. Interobserver agreement for the spine instability neoplastic score varies according to the experience of the evaluator. *Clinics (Sao Paulo)* 2013;68(2):213-218.



3

Clinical evaluation of the Spinal Instability Neoplastic Score in patients treated with radiotherapy for symptomatic spinal bone metastases

Laurens Bollen, Karlijn H.J. Groenen, Willem Pondaag, Carla S.P. van Rijswijk,
Marta Fiocco, Yvette M. van der Linden, Sander P.D. Dijkstra.

Spine 2017;42(16):E956-E962

Introduction

Spinal bone metastases (SBM) develop in up to 70% of cancer patients [1]. Back pain and neurological deficit are the most frequently reported symptoms [2-4]. Current management of SBM focuses on optimizing a patient's quality of life by providing effective pain relief and preserving or restoring neurological function [2]. In addition, spinal instability is a third indication for treatment, as it can lead to the aforementioned symptoms. Whereas patients with stable spines can be treated using non-invasive procedures such as radiotherapy, patients with unstable spines potentially require surgical fixation, either through minimally invasive techniques such as percutaneous stabilization or through more invasive procedures involving open fixation.

Assessment of spinal stability is challenging and is mostly done by relying on clinical experience, in the absence of validated guidelines or an established predetermined set of risk factors. The absence of a standardized approach hinders communication between physicians of different medical specialties and can result in under- as well as overdiagnosis of spinal instability.

In 2010, the Spinal Oncology Study Group introduced the Spinal Instability Neoplastic Score (SINS); the first consensus-based guideline that aids in the assessment of a patient's risk of spinal instability in the setting of neoplastic spinal disease [5]. The SINS determines tumor-related instability based on six criteria and classifies the spinal column as stable, potentially unstable or unstable. Surgical consultation is recommended for patients with a spinal column classified as either potentially unstable or unstable. As such, the SINS facilitates interdisciplinary communication, assesses and categorizes spinal instability, and optimizes treatment decision making.

Previous studies have already shown that the SINS has a substantial to excellent inter-observer and intra-observer reliability [6-9]. Nevertheless, for it to be useful in clinical practice, it should also be evaluated whether the score is indeed predictive of progressive spinal instability when applied to longitudinal patient cohorts. Studies have shown that the total SINS score is not predictive for new or progressive vertebral compression fractures (VCF) in patients receiving high dose stereotactic radiotherapy [10-12]. Therefore, the role of SINS in assessing this specific endpoint is debatable.

The aim of the current study was to determine the predictive value of the total and individual components of the SINS system for spinal instability in a cohort of patients with spinal bone metastases, treated with radiotherapy. Secondly, the inter-observer agreement of both the total categorical SINS score and the individual components was determined.

Patients and methods

All consecutive patients who were treated with radiotherapy for symptomatic SBM between January 2000 and December 2010 in the Leiden University Medical Center, the Netherlands, and also had pretreatment computed tomography (CT) imaging were eligible for inclusion in this retrospective cohort study. In order to ensure accurate correlation between the clinical situation and the obtained images, the maximum accepted time between the diagnostic CT scan and start of treatment was two months. Patients who had already been stabilized were excluded, leaving the patients in whom there is clinical equipoise regarding the best treatment strategy and thus reflecting the more important clinical scenario in daily practice. Only a single metastatically affected vertebra was evaluated per patient. This selection was determined based on inclusion within the radiation field. If multiple vertebrae within the same radiation field were affected by metastatic disease, the vertebra with the highest score on the SINS components location or vertebral body collapse was selected for the analysis.

Each vertebral segment was scored according to the SINS criteria as described by Fisher et al. [5]. The individual SINS components consisted of location (junctional, mobile, semi-rigid, and rigid spine), type of pain (mechanical, non-mechanical, pain-free), type of lesion (lytic, mixed, sclerotic), spinal alignment (subluxation/translation, kyphosis/scoliosis, normal), presence of baseline VCF (>50% collapse, <50% collapse, no collapse but >50% of the body involved, or none of the above), and whether the tumor involved the posterolateral elements (bilateral, unilateral, none). The radiological SINS components bone lesion, alignment, vertebral body collapse, and posterolateral involvement of spinal elements were assessed independently by four expert observers (S.D.; orthopedic surgeon, Y.L.; radiation oncologist, C.R.; radiologist, and W.P.; neurosurgeon). The observers were blinded to the patients' event status. The SINS components pain and location were assessed by one observer (L.B.) based on the patients' clinical files and admission forms. Based on the values for the individual SINS components, the total score was calculated and the spine was classified as being stable, potentially unstable or unstable [5].

Patient characteristics were assessed using de Karnofsky Performance Status (KPS) [13] and the Frankel classification [14]. Expected survival of each individual patient was determined using the Bollen model [15]. Clinical and/or radiological follow-up data for instability was collected until 12 months after initial radiotherapy. The end points of the study were considered adverse events after radiotherapy and consisted of (1) the development of a new pathologic fracture, (2) progression of an existing pathologic fracture, and (3) deterioration of alignment requiring surgical stabilization of the irradiated spinal segments. The occurrence of an adverse event was determined using patients' medical charts and/or follow-up imaging.

Statistical analysis

Inter-observer agreement between all four observers was calculated using Fleiss' kappa [16]. The level of agreement for the obtained kappa was determined according to Landis and Koch [17]. Survival curves were estimated by using the Kaplan-Meier method and follow-up was assessed by using the reverse Kaplan-Meier method [18]. Survival times were calculated as the difference between start of treatment and date of death or last follow-up. Time to event was calculated as the difference between the date of treatment and date of occurrence of an adverse event or last follow-up, with death being considered a competing event. The cumulative incidence for the occurrence of an adverse event at six and twelve months was assessed by using a competing risk model [19]. Sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) were calculated for all observers. The results of the observer with the highest sensitivity and specificity were used to fit univariate and multivariate Fine and Gray models [20], in order to estimate the effect of the risk factors on the cumulative incidence of an event. In order to perform the sensitivity analysis and the Fine and Gray's regression analysis, the final SINS categories were reduced from three to two, aggregating the categories *unstable* and *potentially unstable* versus the category *stable* [7, 8]. A p-value < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 20.0, Armonk, NY and R version 2.18 (R: R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 997 patients were treated with radiotherapy for spinal bone metastases during the study period. Of these, 236 patients underwent a CT scan within two months before starting treatment. Patients without clinical and/or radiological follow-up were excluded and a total of 110 patients remained eligible for analysis.

Table 1 summarizes the characteristics of the study population. Fifty-nine patients (54%) were male and the mean age at the start of treatment was 60.4 years (SD \pm 13.8 years). The Karnofsky Performance Status was normal (100%-80%) in 59 patients (54%) and 107 patients (97%) had no, or only minor motor and sensory deficit. The prognostic category for survival according to the Bollen model was good in six patients (5%), moderate in 28 patients (26%), poor in 57 patients (52%) and very poor in 14 patients (13%). Thirty-six patients (33%) were treated with a single fraction of 8 Gy, 26 patients (24%) with two fractions of 8 Gy and 48 patients (43%) were treated with more than two fractions, totaling a dose of 24 Gy or more.

The overall median survival was 6.6 months (95% confidence interval (CI) 5.5 - 7.7 months) with a median follow-up of 5.2 years. Seventy-nine patients (72%) died within 12 months after starting treatment. A total of 16 patients (15%) experienced an adverse

event during follow-up. Among them, eight patients (50%) experienced a deterioration of spinal alignment for which they were surgically stabilized and eight patients (50%) experienced a pathologic fracture, or progression of their existing fracture. In Figure 1 the cumulative incidence of the two competing events is illustrated. The cumulative incidences for the occurrence of an adverse event at 6 and 12 months were 11.8% (95% CI 5.1% - 24.0%) and 14.5% (95% CI 6.9% - 22.2%), respectively.

Table 1 Patient characteristics.

Characteristic	N (%)
Gender	
Male	59 (54)
Female	51 (46)
Age (years, mean \pm SD)	60.4 \pm 13.8
Primary tumor	
Lung	25 (23)
Breast	18 (16)
Kidney	17 (16)
Colon	14 (13)
Esophagus	9 (8)
Prostate	8 (7)
Other	19 (17)
Karnofsky performance status	
Normal (100-80%)	59 (54)
Impaired (70-10%)	46 (42)
Missing	5 (4)
Frankel classification	
No deficit (E)	67 (61)
Minor motor or sensory deficit (D)	40 (36)
Major motor or sensory deficit (A,B,C)	3 (3)
Expected survival	
A - Good	6 (5)
B - Moderate	28 (26)
C - Poor	57 (52)
D - Very poor	14 (13)
Missing	5 (4)
Total radiotherapy dose	
8 Gy	36 (33)
16 Gy	26 (24)
≥ 24 Gy	48 (43)

Table 2 shows the SINS scores for each individual observer. The level of agreement between all four observers for the final SINS score was moderate ($\kappa = 0.536$, $p < 0.001$). The level of agreement was fair for the components bone lesion ($\kappa = 0.299$, $p < 0.001$) and spinal alignment ($\kappa = 0.358$, $p < 0.001$), whereas the components vertebral body collapse ($\kappa = 0.453$, $p < 0.001$) and posterolateral element involvement ($\kappa = 0.436$, $p < 0.001$) had a moderate level of agreement.

Table 3 shows the sensitivity, specificity, positive predictive value, and negative predictive value of the SINS for all four observers. Sensitivity ranged from 35% - 69%, specificity from 18% - 48%, positive predictive value from 6%-18% and negative predictive value from 63% - 90%.

Table 2 Individual Spinal Instability Neoplastic Score and Fleiss' kappa.

SINS	Kappa	Observer 1 N (%)	Observer 2 N (%)	Observer 3 N (%)	Observer 4 N (%)
Bone lesion	0.299				
Lytic		88 (80)	70 (64)	80 (73)	51 (46)
Mixed		17 (16)	29 (26)	19 (17)	45 (41)
Blastic		5 (4)	11 (10)	11 (10)	14 (13)
Spinal alignment	0.358				
Subluxation/translation		1 (1)	3 (3)	4 (4)	1 (1)
Kyphosis/scoliosis		12 (11)	8 (7)	7 (6)	20 (18)
Normal alignment		97 (88)	99 (90)	99 (90)	89 (91)
Vertebral body collapse	0.453				
>50% Collapse		14 (13)	15 (14)	16 (15)	14 (13)
<50% Collapse		27 (24)	41 (37)	28 (25)	49 (44)
None, >50% involvement		22 (20)	14 (13)	39 (36)	23 (21)
None of the above		47 (43)	40 (36)	27 (24)	24 (22)
Posterolateral elements	0.436				
Bilateral		12 (11)	27 (25)	43 (39)	23 (21)
Unilateral		28 (25)	43 (40)	36 (33)	24 (22)
None		70 (64)	40 (36)	31 (28)	63 (57)
Location*	-				
Junctional		50 (55)	50 (55)	50 (55)	50 (55)
Mobile spine		25 (23)	25 (23)	25 (23)	25 (23)
Semi-rigid		35 (32)	35 (32)	35 (32)	35 (32)
Rigid		0 (0)	0 (0)	0 (0)	0 (0)
Pain*	-				
Yes; mechanical pain		24 (22)	24 (22)	24 (22)	24 (22)
Yes; non-mechanical pain		80 (73)	80 (73)	80 (73)	80 (73)
No		6 (5)	6 (5)	6 (5)	6 (5)
Total SINS score	0.536				
Stable (0-6 points)		50 (46)	41 (37)	31 (28)	37 (34)
Uncertain (7-12 points)		55 (50)	63 (57)	70 (64)	70 (63)
Unstable (13-18 points)		5 (4)	6 (6)	9 (8)	3 (3)

*Variables location and pain were determined separately and therefore identical among all four observers.

SINS: Spinal Instability Neoplastic Score.

Table 3 Evaluation of the Spinal Instability Neoplastic Score accuracy.

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Observer 1	69	48	18	90
Observer 2	35	27	7	71
Observer 3	35	18	6	63
Observer 4	41	25	8	71

PPV: positive predictive value; NPV: negative predictive value

Univariate Fine and Gray analysis showed that the final SINS classification, total radiotherapy dose, as well as the six individual SINS components were not significantly associated with the cumulative incidence of an event (Table 4). The multivariate analysis included all six SINS components as well as total radiotherapy dose. Only the component *location* was significantly associated with the cumulative incidence of an adverse event with a hazard ratio of 0.54 (95% CI 0.30 - 0.96, $p = 0.04$) (Table 4).

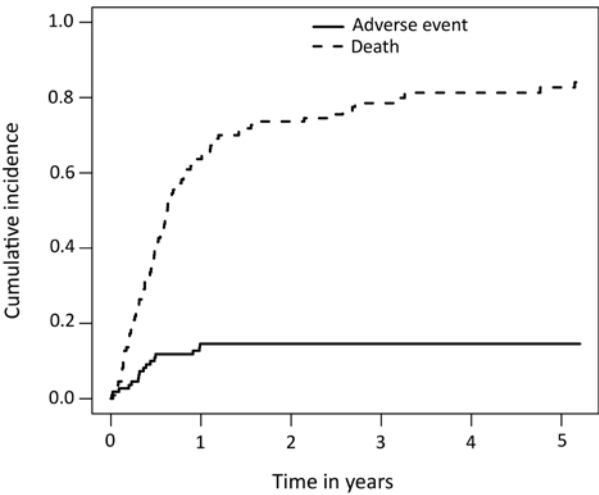


Figure 1 Cumulative incidence of adverse events and death for the entire cohort.

Table 4 Results of the univariate and multivariate Fine and Gray models.

Univariate Fine and Gray	HR	95% CI	p-value
Location	0.71	0.42-1.31	0.22
Pain	0.53	0.22-1.13	0.09
Bone lesion	1.90	0.33-10.89	0.47
Spinal alignment	1.01	0.53-1.95	0.97
Vertebral body collapse	0.96	0.61-1.51	0.85
Posterolateral elements	1.28	0.86-1.90	0.22
Total SINS score	2.01	0.73-5.62	0.19
Total dose	1.02	0.96-1.07	0.53
Multivariate Fine and Gray	HR	95% CI	p-value
Location	0.54	0.30-0.96	0.04
Pain	0.40	0.13-1.17	0.10
Bone lesion	1.32	0.25-7.02	0.75
Spinal alignment	1.06	0.46-2.40	0.90
Vertebral body collapse	0.64	0.32-1.29	0.21
Posterolateral elements	1.15	0.64-2.08	0.65
Total dose	1.01	0.95-1.08	0.79

HR: Hazard ratio; CI: Confidence interval; SINS: Spinal Instability Neoplastic Score

Discussion

In this single-center retrospective study it is demonstrated how the SINS performs on an independent dataset consisting of 110 patients undergoing external beam radiation therapy for symptomatic SBM. Competing risk analysis showed that the SINS classification was not significantly associated with the cumulative incidence of an adverse event within the studied population.

The levels of agreement found in this study were obtained by calculating Fleiss' kappa based on the results of four highly experienced observers and ranged from fair to moderate. The results were comparable to those obtained in previous studies [6, 8, 9]. Especially the SINS component *bone quality*, describing the lesion as being lytic, blastic, or mixed, continues to be a challenge for observers to agree upon, ranging from only 0.21 to 0.30 [6, 8, 9].

Apparently, although seemingly objective, measures such as displacement and kyphosis are still difficult to interpret, even for highly experienced clinicians. Previous research comparing the inter-observer agreement between groups of similar specialist (e.g. orthopedic surgeons *versus* no orthopedic surgeons and surgeons *versus* radiation oncologists), has shown that the clinicians' background seems to affect their agreement on the total SINS score as well as different components of the SINS [7, 9]. Accordingly, a mixed group of clinicians agrees less than, for example, a group of experienced orthopedic surgeons. It has also been shown that experience affects the degree of agreement. Highly experienced spine surgeons agree more than less experienced spine surgeons [9].

The highest levels of sensitivity and specificity found in this study (69% and 48%) differed considerably when compared to the levels found in the study performed by Fourney et al. (96% and 80%) [8]. This might be attributed to the fact that Fourney et al. used consensus opinion to *a priori* define a metastatic spine as either stable or unstable, whereas in this study actual clinical endpoints were used to define stable and unstable spines. Nonetheless, a sensitivity of 69% suggests a good capacity to identify patients with a low risk of complication due to spinal instability. In clinical practice, this could translate to fewer surgical consultations for patients who are classified as *stable* according to the SINS. On the other hand, the rather low specificity found in this study indicates that no treatment decisions should be made based on the classifications *potentially unstable* and *unstable*. In daily practice, surgical consultation is still warranted for these categories.

In line with previously reported studies [10, 11], no predictive value of the total SINS score was observed for the occurrence of an adverse event. Total radiotherapy dose and the individual SINS components, *pain*, *bone lesion*, *alignment*, *collapse* and *posterolateral involvement* did not show a significant association with the occurrence of an adverse event in the multivariate analysis. Even though the component *location* reached a significant level of association, a hazard ratio of less than one is indicative of a

protective effect for developing spinal instability, rather than a harmful effect, as implied by the SINS. As a result, this variable might not provide any clinically relevant information when assessing spinal instability.

Similar to our study, Lam et al. [21] retrospectively examined the relationship of the SINS and dose fractionation with the development of a spinal adverse event (SAE) in 299 patients with SBM who received radiotherapy. They found that a SINS score of 11 or greater and a single fraction of 8 Gy were independent predictors for the development of an SAE. The definition of an event was, however, much broader than in the present study. For instance, hospitalization due to pain at the irradiated site was considered an SAE, constituting 37% of all events. It is unlikely that the SINS can evaluate hospitalization due to pain and including it as an adverse event could potentially obscure the results.

In contrast to our study, Cunha et al. [10] found an association between the components *spinal alignment* and *lesion type* on the occurrence of a VCF and Sahgal et al. [11] found an association between *spinal alignment*, *lesion type* and *vertebral body collapse* on the occurrence of a VCF. The major difference is that these two studies reported on patients who underwent high-dose stereotactic radiotherapy, potentially resulting in more VCFs, whereas the population in this study underwent relatively low-dose radiotherapy.

A limitation of the current study is the retrospective design. The SINS component *pain* was determined based on patient charts and intake forms, possibly resulting in inaccurate interpretation of the data. The availability of pretreatment CT scans was limited (236/997, 24%), reducing the overall population count.

Although patients who presented with evident clinical spinal instability and were operated on are not represented in the present study, our analysis reflects the more important daily clinical scenario. The main treatment for patients with painful bone metastases is radiotherapy. Since these patients have limited survival, spinal surgery must only be applied in case of a reasonable and stable clinical condition. One aims to prevent that patients treated with radiotherapy will undergo an adverse event in their follow-up. Thus, especially in this heterogeneous patient group in terms of, among others, primary tumor, physical condition, and referring physician, in which a limited risk of spinal instability is expected, it is of utmost importance to identify those patients who, after radiotherapy, underwent an event and perhaps would have gained more in terms of sustaining quality of life if a surgical stabilizing procedure had been performed instead of radiotherapy. By including only patients treated with radiotherapy, we focused on this clinically important group in which there is some clinical equipoise. Therefore, leaving out patients who were primary stabilized did not result in major selection bias.

Strengths of the study are the number of observers and the fact that highly experienced clinicians of four different medical disciplines involved with treatment of SBM were represented. Although there was limited agreement between the four observers, our panel's constitution reflects clinical practice as in everyday reality spinal

instability is often assessed separately by individual clinicians. Although a multidisciplinary meeting would seem most fitting to discuss instability and agree on appropriate treatment, due to the often swift course of disease and symptoms, such weekly meetings take place too late. Also, the endpoints used are clinically relevant. Whereas other validation studies compared the SINS outcome to predetermined consensus-based cases of stable and unstable spines, in the current study, actual clinical data were used as outcome measure.

Even though the authors agree that the components constituting the SINS classification are potentially important factors to consider when assessing spinal instability, in its current form, clinical applicability seems limited. As a tool for streamlining communication between physicians of different medical specialties and facilitating the decision making concerning surgical consultation, the SINS could be useful.

A prospective CT-based study with clear clinical endpoints might help to determine the relative importance of each component in predicting complications resulting from spinal instability and could result in an adjustment of the points allocated to each component, as well as the grouping of each variable. As the present study and the study performed by Teixeira et al. [9] have shown, panels consisting of reviewers from different medical specialties can result in lower levels of agreement, whereas a panel consisting of observers from one specialty can result in very high levels of agreement [7]. Therefore, the optimal reviewing panel for such a study remains to be determined, but it seems observers from a surgical specialty generally have the highest level of agreement.

In conclusion, this study provides an insight into the ability of the SINS to assess spinal instability in patients undergoing external beam radiation therapy for spinal bone metastases. Based on these results, the clinical applicability of the SINS as a tool to assess spinal instability seems limited.

References

1. Coleman RE. Metastatic bone disease: clinical features, pathophysiology and treatment strategies. *Cancer Treat Rev* 2001;27(3):165-176.
2. Bartels RH, van der Linden YM, van der Graaf WT. Spinal extradural metastasis: review of current treatment options. *CA Cancer J Clin* 2008;58(4):245-259.
3. Loblaw DA, Perry J, Chambers A, Laperriere NJ. Systematic review of the diagnosis and management of malignant extradural spinal cord compression: the Cancer Care Ontario Practice Guidelines Initiative's Neuro-Oncology Disease Site Group. *J Clin Oncol* 2005;23(9):2028-2037.
4. Perrin RG. Metastatic tumors of the axial spine. *Curr Opin Oncol* 1992;4(3):525-532.
5. Fisher CG, DiPaola CP, Ryken TC, Bilsky MH, Shaffrey CI, Berven SH, Harrop JS, Fehlings MG, Boriani S, Chou D, Schmidt MH, Polly DW, Biagini R, Burch S, Dekutoski MB, Ganju A, Gerszten PC, Gokaslan ZL, Groff MW, Liebsch NJ, Mendel E, Okuno SH, Patel S, Rhines LD, Rose PS, Sciubba DM, Sundaresan N, Tomita K, Varga PP, Vialle LR, Vrionis FD, Yamada Y, Fourny DR. A novel classification system for spinal instability in neoplastic disease: an evidence-based approach and expert consensus from the Spine Oncology Study Group. *Spine (Phila Pa 1976)* 2010;35(22):E1221-1229.
6. Campos M, Urrutia J, Zamora T, Roman J, Canessa V, Borghero Y, Palma A, Molina M. The Spine Instability Neoplastic Score: an independent reliability and reproducibility analysis. *Spine J* 2014;14(8):1466-1469.
7. Fisher CG, Schouten R, Versteeg AL, Boriani S, Varga PP, Rhines LD, Kawahara N, Fourny D, Weir L, Reynolds JJ, Sahgal A, Fehlings MG, Gokaslan ZL. Reliability of the Spinal Instability Neoplastic Score (SINS) among radiation oncologists: an assessment of instability secondary to spinal metastases. *Radiat Oncol* 2014;9:69.
8. Fourny DR, Frangou EM, Ryken TC, DiPaola CP, Shaffrey CI, Berven SH, Bilsky MH, Harrop JS, Fehlings MG, Boriani S, Chou D, Schmidt MH, Polly DW, Biagini R, Burch S, Dekutoski MB, Ganju A, Gerszten PC, Gokaslan ZL, Groff MW, Liebsch NJ, Mendel E, Okuno SH, Patel S, Rhines LD, Rose PS, Sciubba DM, Sundaresan N, Tomita K, Varga PP, Vialle LR, Vrionis FD, Yamada Y, Fisher CG. Spinal instability neoplastic score: an analysis of reliability and validity from the spine oncology study group. *J Clin Oncol* 2011;29(22):3072-3077.
9. Teixeira WG, Coutinho PR, Marchese LD, Narazaki DK, Cristante AF, Teixeira MJ, Barros Filho TE, Camargo OP. Interobserver agreement for the spine instability neoplastic score varies according to the experience of the evaluator. *Clinics (Sao Paulo)* 2013;68(2):213-218.
10. Cunha MV, Al-Omair A, Atenafu EG, Masucci GL, Letourneau D, Korol R, Yu E, Howard P, Lochray F, da Costa LB, Fehlings MG, Sahgal A. Vertebral compression fracture (VCF) after spine stereotactic body radiation therapy (SBRT): analysis of predictive factors. *Int J Radiat Oncol Biol Phys* 2012;84(3):e343-349.
11. Sahgal A, Atenafu EG, Chao S, Al-Omair A, Boehling N, Balagamwala EH, Cunha M, Thibault I, Angelov L, Brown P, Suh J, Rhines LD, Fehlings MG, Chang E. Vertebral compression fracture after spine stereotactic body radiotherapy: a multi-institutional analysis with a focus on radiation dose and the spinal instability neoplastic score. *J Clin Oncol* 2013;31(27):3426-3431.
12. Sung SH, Chang UK. Evaluation of risk factors for vertebral compression fracture after stereotactic radiosurgery in spinal tumor patients. *Korean J Spine* 2014;11(3):103-108.
13. Karnofsky DA, Abelmann WH, Craver LF, Burchenal JH. The Use of the Nitrogen Mustards in the Palliative Treatment of Carcinoma - with Particular Reference to Bronchogenic Carcinoma. *Cancer* 1948;1(4):634-656.
14. Frankel HL, Hancock DO, Hyslop G, Melzak J, Michaelis LS, Ungar GH, Vernon JD, Walsh JJ. The value of postural reduction in the initial management of closed injuries of the spine with paraplegia and tetraplegia. I. Paraplegia 1969;7(3):179-192.
15. Bollen L, van der Linden YM, Pondaag W, Fiocco M, Pattynama BP, Marijnen CA, Nelissen RG, Peul WC, Dijkstra PD. Prognostic factors associated with survival in patients with symptomatic spinal bone metastases: a retrospective cohort study of 1,043 patients. *Neuro Oncol* 2014;16(7):991-998.
16. Fleiss JL, Cohen J. Equivalence of Weighted Kappa and Intraclass Correlation Coefficient as Measures of Reliability. *Educ Psychol Meas* 1973;33(3):613-619.

17. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics* 1977;33(1):159-174.
18. Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. *Control Clin Trials* 1996;17(4):343-346.
19. Putter H, Fiocco M, Geskus RB. Tutorial in biostatistics: competing risks and multi-state models. *Stat Med* 2007;26(11):2389-2430.
20. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 1999;94(446):496-509.
21. Lam TC, Uno H, Krishnan M, Lutz S, Groff M, Cheney M, Balboni T. Adverse Outcomes After Palliative Radiation Therapy for Uncomplicated Spine Metastases: Role of Spinal Instability and Single-Fraction Radiation Therapy. *Int J Radiat Oncol Biol Phys* 2015;93(2):373-381.



4

Inducing targeted failure in cadaveric testing of 3-segment spinal units with and without simulated metastases

Karlijn H.J. Groenen, Dennis Janssen, Yvette M. van der Linden, Jan G.M. Kooloos,
Jasper Homminga, Nico Verdonchot, Esther Tanck.

Medical Engineering and Physics 2018;51:104-110

Introduction

Spinal bone metastases compromise the structural integrity of vertebral bone tissue and thus negatively affect vertebral bone strength and increase the risk of pathological fractures. Pathological vertebral fractures are accompanied by severe pain and can lead to spinal deformations and neurological complications such as spinal cord compression [1, 2], all of which have a significant and negative impact on the quality of life [3, 4].

To study bone strength, *in vitro* compression experiments can be used. In such experiments, cadaveric vertebral bones are mechanically loaded until failure. In previous *in vitro* studies, vertebral strength has mostly been established via experiments using single vertebral bodies [5-8], single vertebrae [9-12], and functional spinal units [13]. However, the simplified loading conditions applied to one vertebra (or just its body) are bound to introduce loading artifacts. A more physiological loading condition can be obtained by using 3-segment spinal units, consisting of three consecutive vertebrae and two intervertebral discs. In this way, the (middle) target vertebra is loaded via two intervertebral discs, the posterior elements including the facet joints, and the spinal ligaments. Although using a 3-segment spinal unit considerably improves the simulation of physiological loading conditions, it makes the experiment more complex compared to testing a single vertebra. This complexity might be the reason why only few studies on vertebral strength have been performed using 3-segment spinal units with intact posterior elements [14-19].

It is beneficial to capture the deformation of specimens in their post-failure state, particularly when the experiments are also used to validate finite element (FE) models. For this, the loading of the specimens should be halted as soon as fracture in the target vertebrae occurs, to prevent the specimens from being fully destroyed. However, as it is difficult to observe actual failure during the experiment, it is important to define a clear and reliable failure criterion. In previous studies a clear drop in force (>10 - 15% of peak force) has been used as failure criterion in 3-segment spinal units, with or without intact posterior elements [14, 20, 21]. However, generally these studies did not verify whether a true fracture or collapse actually occurred with this criterion.

Despite the extensive body of work, there currently are no experiments in which 3-segment spinal units with intact posterior elements are loaded only *until* initial failure. The objective of our study was to develop an experimental setup and protocol able to induce targeted failure of the middle vertebra in 3-segment spinal units and to capture the specimens' deformation at their post-failure state. In this technical note, we share the lessons we have learned while developing this experimental setup.

Ideally, not only should the experimental setup and protocol be suitable for studying 'healthy' vertebrae, it should also be applicable for e.g. testing metastatic or osteoporotic vertebrae and investigating effects of treatments such as vertebroplasty, kyphoplasty, tumor ablation, and spinal cages. Next to testing healthy vertebrae, we chose to simulate lytic metastatic lesions in half the number of spinal segments.

Our first experimental protocol used the clear drop in force (>10-15% of peak force) failure criterion, which is commonly used by others [14, 20, 21]. After evaluation of the first set of experiments it was shown that this failure criteria did not sufficiently result in targeted failure of the middle vertebrae. Therefore, we subsequently introduced a new failure criterion that was applied to a second set of experiments. In this paper, we describe the setup and protocol as well as results of both experimental attempts.

Methods

Specimen preparation

Four complete spines were obtained from fresh frozen cadavers (3 men, 1 woman; aged 63 - 92 years). The specimens were obtained from the Department of Anatomy with institutional approval. An experienced orthopedic surgeon reviewed anteroposterior X-rays of the four spines to confirm the absence of fractures and collapses in the thoracic and lumbar spine, malignancies in the vertebrae, surgery to the spine, and scoliosis. The spines were not screened for osteoporosis.

With the help of an experienced anatomist, each spine was sectioned into four 3-segment spinal units (T6-T8, T9-T11, T12-L2, and L3-L5) (Table 1). The specimens were cleaned from soft tissues, while carefully preserving the facet capsules, intervertebral discs, and spinal ligaments. In case of thoracic units, the costovertebral joints were kept intact by dissecting the costae approximately 5 cm distally of the costovertebral joints. The ribs of the upper vertebrae of each specimen were completely removed, to allow placement in the test setup. After dissection, the specimens were hydrated, wrapped in towels, sealed in a plastic bag and stored at -20°C until mechanical testing.

Simulated lytic metastatic lesions

Specimens were thawed prior to testing and experiments were performed at room temperature. The specimens were kept moist with saline spray mist throughout preparation and testing. In half of the specimens, we simulated metastatic lesions in the middle vertebral bodies (Figure 1). In order to minimize spinal-level bias, the specimens with a simulated lesion were chosen alternately superior and inferior with respect to those without a lesion (Table 1: 'lesion (L)' and 'control (C)', respectively). The lesions were created through the lateral removal of a cylindrical core of cortical and cancellous bone in the posterior part of the vertebral body. With the help of experienced clinicians, this posterior location was chosen as it is the preferred site of initial tumor seeding [22, 23]. In addition, lesions in the posterior part of the vertebral body are believed to elevate burst fracture risk [24] and subsequent retropulsion of bone fragments with spinal cord or cauda equine compression, a common clinical finding.

Table 1 Overview of the tested specimens. The first set of experiments consisted of 4 specimens (A1-A4); the second set of experiments consisted of 12 specimens (B1-D4).

Experiment	Sex (M/F)	Age at death [y]	Weight [kg]	Length [cm]	BMI [kg/m ²]	Specimen	Lesion (L) / Control (C)	Successful (S) / Unsuccessful (U) experiment	Failure load [N]
A	M	63	88	191	24.0	A1 T6-T8	C	U	-
						A2 T9-T11	L	S	3091
						A3 T12-L2	L	S	2178
						A4 L3-L5	C	U	-
B	F	80	44	157	17.9	B1 T6-T8	C	S	3232
						B2 T9-T11	L	S	2573
						B3 T12-L2	L	S	2339
						B4 L3-L5	C	S	3929
	M	92	87	187	24.9	C1 T6-T8	L	S	3307
						C2 T9-T11	C	U	-
						C3 T12-L2	C	S	3294
						C4 L3-L5	L	S	2474
	M	80	55	163	20.7	D1 T6-T8	C	U	-
						D2 T9-T11	L	S	1386
						D3 T12-L2	L	S	1275
						D4 L3-L5	C	U	-

To avoid bias due to lesion size, the relative size of the lesion was kept constant between specimens: the depth of the lesion comprised 75% of the maximal vertebral body width and its diameter 55% of the maximal vertebral body height (Figure 1). The most posterior aspect of the lesion was aimed at 5 mm from the posterior vertebral body wall. The vertebrae's dimensions were measured on full body computed tomography (CT) scans (Somatom Sensation 64, Siemens Healthcare, Erlangen, Germany; resolution ranging from 0.35 x 0.35 x 0.6 mm to 0.38 x 0.38 x 1.0 mm). The resulting defect was filled with 0.5% solution of agarose gel formulated to mimic the average material properties of lytic tumor specimens as defined by Whyne et al. [25, 26]. Whyne et al. tested human lytic tumor specimens under a confined compression uniaxial creep protocol and modeled the mechanical behavior of the tumor tissue using linear biphasic theory. The tumor tissue was found to have an aggregate modulus (H_A) of 3.6 ± 1.6 kPa and a hydraulic permeability (k) of 0.59 ± 0.46 mm⁴N⁻¹s⁻¹. The removed core was dissected to isolate the cortical cap, which was reattached with polymethylmethacrylate (PMMA) to seal the lesion inside the vertebral body [25].

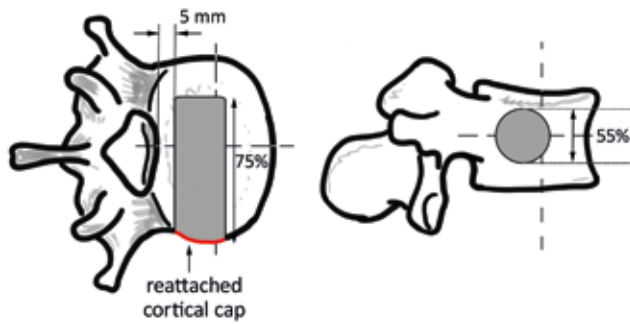


Figure 1 Size and location of the simulated metastatic lesions.

Mechanical experiment

After simulating the metastatic lesions in the vertebrae, we embedded the outer vertebrae of each specimen in PMMA, such that the mid-transverse planes of the middle vertebral bodies were horizontal (Figure 2). Radiographs from both the anteroposterior and mediolateral view were taken during the mounting process to confirm the orientation of the specimens. The embedded specimens were CT scanned (Aquilion/CXL, Toshiba Medical, Otawara, Japan; resolution 0.6 x 0.6 x 0.6 mm) while submerged in a water basin. Subsequently, to be able to fixate the specimens at their final loading states, the specimens were placed in a plastic bag before mounting them in a hydraulic testing machine (MTS Systems Corporation, Eden Prairie, Minnesota, United States). Each specimen was mounted in the testing machine, such that the center of the middle vertebral body was aligned with the loading axis (Figure 2). The correct position of the

specimen with respect to the loading pin was ensured using anteroposterior and mediolateral radiographs. The lower vertebra was constrained from translations and rotations in any direction. In contrast, free rotation in all directions was allowed for the upper vertebra. This way, initially a pure compressive force was applied, but once the loading of the specimens started, the specimens were allowed to 'pivot' around the load application point.

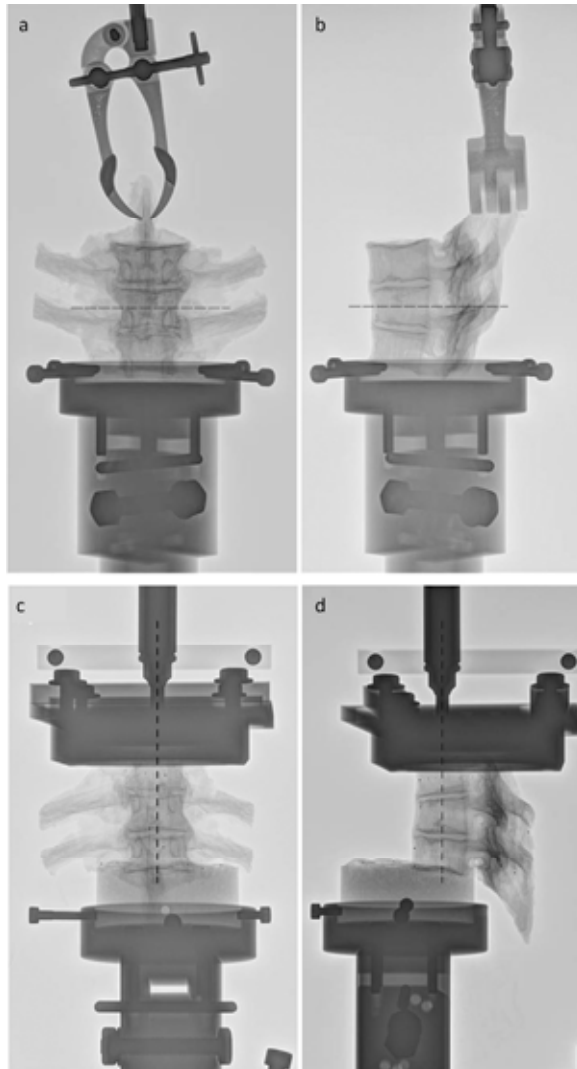


Figure 2 The outer vertebrae of each specimen were embedded in PMMA, such that the mid-transverse planes of the middle vertebral bodies were horizontal. The correct position was ensured using anteroposterior (a) and mediolateral (b) radiographs. When placing the specimen in the MTS machine, the center of the vertebral body was aligned with the loading axis. The correct position of the specimen with respect to the loading pin was ensured using anteroposterior (c) and mediolateral (d) radiographs.

Preconditioning of the specimens consisted of cyclically, incrementally loading the specimens from 0 to 300 N, with 50 N increments. Following preconditioning, specimens were destructively tested in axial compression at 2 mm/min, while registering force (uniaxial, 10 kN load cell, Model 3173, InterTechnology Inc., Toronto, Canada) and displacement of the plunger (100 Hz). As soon as failure (defined by one of the two specific failure criteria) had occurred, the loading was paused. In two consecutive sets of experiments, two different failure criteria were used (see Methods – Failure criteria).

Failure criteria

Failure criterion A: clear drop in force

In our first set of experiments (specimens A1-A4; Table 1), we used the failure criterion that has been used in previous failure experiments with 3-segment spinal units: a clear drop in force ($>10 - 15\%$ of peak force) [14, 20, 21]. After observing such a drop in the recorded force, the loading was immediately paused.

Failure criterion B: minimum applied displacement of 5 mm

In experiment A we paused the loading immediately after a drop in force was observed. When evaluating the first set of experiments (see Results - Failure criterion A: clear drop in force) it was, however, shown that failure criterion A did not sufficiently result in targeted failure of the middle vertebrae. Therefore, we changed the failure criterion. The applied displacements at pausing the loading in experiment A were 2.1 mm (A1); 3.6 mm (A2); 2.6 mm (A3); and 4.3 mm (A4). For criterion B we decided to apply a minimum of 5 mm displacement, being approximately twice as much as the observed displacement at pausing the loading, to increase the likelihood of inducing failure. At the same time, the specimens needed to be prevented from being fully crushed, as verifying targeted failure is no longer possible in fully crushed specimens. Therefore, we set a maximum applied displacement to 10 mm. In the second set of experiments (specimens B1-D4; Table 1) loading was paused if one of the following conditions was reached:

1. The displacement was 5 mm and a clear drop in force, or a flattening of the force signal had occurred before the 5 mm limit, or;
2. A clear drop in force, or flattening of the force signal was observed after the 5 mm displacement limit, or;
3. A displacement of 10 mm was reached.

Verification of the occurrence of failure

To determine whether vertebral failure had occurred, CT scans of fully fixated specimens in their final loading position were generated and compared to the specimens' pre-experimental CT scans. To both facilitate fracture detection and to capture the specimens' post-failure state, the specimens were fixated by embedding them in PMMA

that was contained by a plastic bag, while the specimens were in the final loading position (Figure 3). Post-experiment CT images (Aquilion/CXL, Toshiba Medical, Otawara, Japan) were acquired (resolution 0.6 x 0.6 x 0.6 mm). Pre- and post-experiment CT scans were evaluated by an experienced radiologist to determine the occurrence of a fracture and/or collapse in one of the vertebral bodies. Experiments in which only the middle vertebra had failed were defined as successful. In contrast, experiments in which the upper or lower vertebrae failed, either or not in combination with the middle vertebrae, were defined as unsuccessful. For the successful experiments, we determined the experimental load to failure from the force-displacement curves.

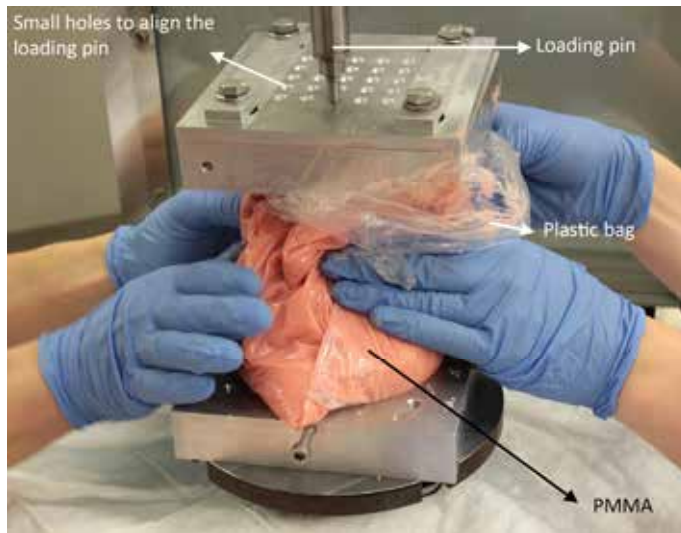


Figure 3 Each specimen was mounted in the testing machine, such that the center of the middle vertebral body was aligned with the loading axis. The small holes in the upper part of the test setup allowed moving the loading pin to have the correct alignment of the spinal segment and loading pin. The specimens were fixated in their post-failure state by fully embedding the specimens in PMMA.

Results

All specimens were successfully loaded and fixated in their post-failure state and further analyzed. Data from all specimens and failure criteria are summarized in Table 1 and Figures 4 to 6.

Failure criterion A: clear drop in force

Four specimens (A1-A4) were tested following this protocol. We experienced difficulties in monitoring the relative drop in force during each measurement and at the same time

preventing the specimens from being fully destroyed. As a result, it appeared that two experiments were halted prematurely. In specimens A1 and A3, a major drop in force was observed (resp. -18% and -58%), while in A2 and A4 only a minor drop in force was seen (resp. -3.6% and -6.8%) (Figure 4). Radiological evaluation showed that fracture of the target vertebra occurred in specimens A2 and A3, which were both specimens with a simulated lesion. Thus, although we observed a clear drop in force in specimens A1 and A3, only specimen A3 showed a fracture on the CT images: the lower border of the middle vertebral body fractured just below the simulated lesion, shown by a disruption of the cortex (Figure 5). The vertebral body height had not changed. In addition, even though we saw only a minor drop in force in specimens A2 and A4, the middle vertebral body of specimen A2 did collapse with a corresponding decrease in vertebral body height (Figure 5). None of the vertebral bodies of the control specimens (A1 and A4) fractured or collapsed, despite the clear drop in force.

The failure load of the successful experiments were 2178 and 3091 Newton (N) (Table 1).

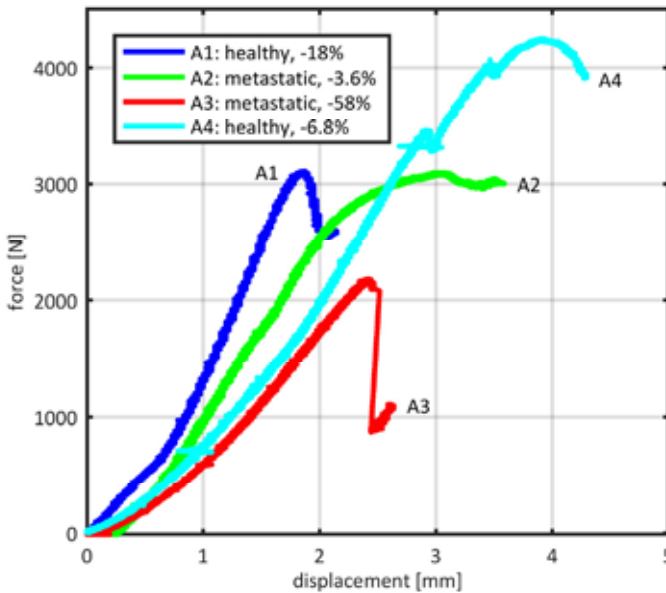


Figure 4 Force displacement curves of the four specimens tested with failure criterion A. Drops in force are depicted [%].

Failure criterion B: minimum applied displacement of 5 mm

In the second set of experiments, 12 specimens were mechanically tested using the newly formulated failure criterion. Radiological examination revealed that in nine out of these 12 experiments only the middle vertebrae fractured or collapsed (Figure 6). Thus,

according to this failure criterion, 75% of the experiments were successful. In the other three specimens, either the lower vertebra ($n = 1$; C2), or both the middle and lower vertebrae ($n = 2$; D1, D4) showed signs of failure. The experimental success rate for specimens with simulated lesions was 100% and for the control vertebrae 50%.

The failure load of the metastatic and control specimens ranged from 1275 N to 3307 N and from 3232 N to 3929 N, respectively (Table 1). All but one specimens with a simulated metastatic lesion had a lower load to failure than the control specimens.

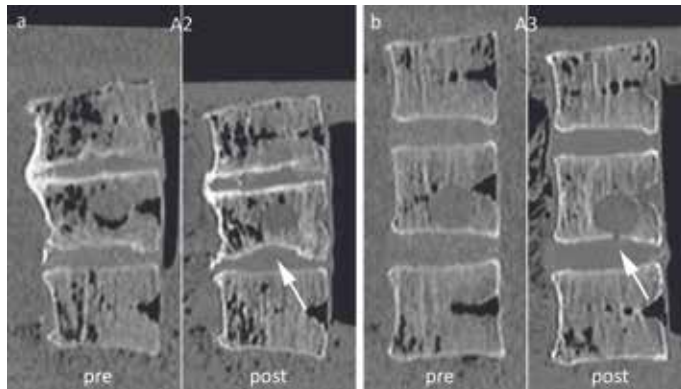


Figure 5 Radiological evaluation showed that fracture of the target vertebra occurred in specimens A2 (a) and A3 (b). The arrows indicate the vertebral body collapse and cortex disruption in specimens A2 and A3, respectively. Only the vertebral bodies are shown.

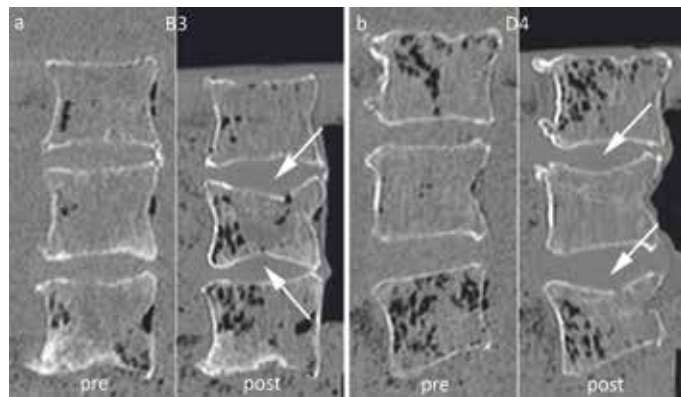


Figure 6 Radiological examination of pre- and post-experiment CT scans revealed that in 9 out of 12 experiments only the middle vertebrae fractured or collapsed. The pictures show representative specimens of successful (a; specimen B3) and unsuccessful (b; specimen D4) experiments. The arrows indicate the vertebral deformation. Only the vertebral bodies are shown.

Discussion

The goal of this study was to develop an experimental setup and protocol able to induce targeted failure of the middle vertebra in 3-segment spinal units with intact posterior elements and to capture the specimens' deformation in their post-failure state. To this end, we mechanically loaded 3-segment spinal units with and without simulated metastatic lesions in compression and applied two different failure criteria. First we applied the clear drop in force failure criterion (failure criterion A), which is a common approach in previous research [14, 20, 21]. An interim evaluation showed that failure criteria A did not sufficiently result in targeted failure of the middle vertebrae. Therefore, we proposed and applied a new failure criterion based on the results obtained in the first experiment, being a minimum applied displacement of 5 mm. In addition, we developed a simple method to capture the specimens' deformation at initial failure.

In the first set of experiments, we applied the clear drop in force ($>10 - 15\%$ of peak force) failure criterion, which has been suggested in literature when using 3-segment spinal units [6, 14, 21]. It appeared to be difficult to monitor the relative drop in force during running experiments. As a result, post-testing examination of the force-displacement curves illustrated that a $>10\%$ drop in force was not achieved in all experiments. Although based on only four specimens, the current results also showed that a clear drop ($>10\%$) in force did not necessarily indicate failure of the target vertebral body. In fact, also a minor drop in force (in our case 3.6%) could indicate a vertebral body collapse. Based on these observations, the occurrence of failure of the middle vertebral body cannot be assumed when using the clear ($>10\%$) drop in force failure criterion; failure should be verified post-testing.

After changing the failure criterion to a minimum applied displacement of 5 mm, radiological examination indicated more experiments to be successful for this criterion, as in 9 out of 12 tests only the middle vertebrae fractured or collapsed. Therefore, loading the specimens with at least 5 mm displacement increased the probability of inducing fractures in the middle vertebrae.

Making the failure criterion of 5 mm displacement parametric rather than dependent on an absolute distance, might enhance the general applicability of this failure criterion. We have investigated the relation between the height of the 3-segment spinal units and the amount of displacement applied at the moment of failure. However, there appeared to be no correlation (data not shown). Although making the criterion parametric is an interesting and valuable approach, vertebral failure is very likely a multifactorial event, not only depending on spinal segment height. Factors such as bone quality, age, body length, BMI, spinal level, and 3-dimensional size of the vertebrae may also play a role. Determining the relevant factors would require a substantial larger amount of experimental specimens to be tested.

All experiments that were unsuccessful, i.e. experiments in which not only the middle vertebrae showed signs of failure, in the second set of experiments involved specimens without a simulated metastatic lesion. The experimental success rate for simulated lesions was 100% and for control vertebrae 50%. This shows how difficult it is to enforce failure of the middle vertebra and one can question whether our experimental protocol including failure criterion B is suitable for testing intact vertebrae. Therefore, we suggest to halt loading immediately after failure, in order to fixate (or 'freeze') the specimen and to subsequently verify, using imaging, whether indeed only one vertebra failed during the experiment. If so, it can be assumed that the measured failure load corresponds to the strength of that particular vertebra.

Overall, the failure loads found in this study ranged between 1275 N and 3929 N. Previous studies in which 3-segment spinal units, either with simulated spinal metastases or not, were loaded until failure reported failure loads ranging from approximately 500 N to 8000 N [14-18]. Thus, the failure loads obtained in the current study fall well within the range previously reported. However, all these studies slightly differ in terms of failure criterion used, verification of inducing targeted failure, and in experimental setup and protocol used. Therefore, one can argue whether directly comparing the results of the current study with previous studies is a valid approach.

Fully fixating the specimens in PMMA in their post-failure state and, subsequently, acquiring CT scans post-loading is a simple solution to verify the occurrence of failure and assess the failure mode. Previous studies have used fluoroscopy to examine deformation of vertebrae in real-time while mechanically loading them and to determine whether or not fracture has occurred [17, 18]. However, besides logistical difficulties (e.g. the availability of both fluoroscope and qualified operator), when the specimens are loaded quasi statically (2 mm/min) bony changes occur so slowly that they are hard to observe by eye. Radiographs have also been used to investigate the site of failure [15, 16]. Both radiographs and fluoroscopy are not ideal to evaluate vertebral failure due to their limited spatial resolution and inability to view the specimens in 3D. Computed tomography scanning is the preferred imaging modality for evaluating the osseous spine in clinical practice. Fully fixating the specimens in PMMA did not affect the quality of the CT images; the radiologist was not hampered by the PMMA surrounding the specimens while evaluating the post-experiment bone status of the specimens. For these reasons, fully fixating the specimens in PMMA while in initial failure state and acquiring CT scans is a good and simple solution to verify the occurrence of failure.

Pre- and post-experimental CT scans also allow for the quantification of the three-dimensional (3D) deformation of the entire specimen. This, for example, is of great value when experiments are used to validate FE models. In that case, the calculated entire specimen deformation can serve, next to failure load or the force-displacement curve, as a validation for plastic deformation predicted by the FE simulation.

Recent advances in CT-technology allow for executing the experiment within a CT scanner. Alkalay et al. reported on a CT-compatible mechanical test system

(compression: 0 - 4000 N; displacement 0 - 50 mm) to image the deformation of a T12-L1 motion segment and measure the change in strain response under compressive loads ranging from 50 to 750 N [27]. The major benefit of such a CT compatible experimental setup is that multiple CT scans can be generated over time. However, the load should be held for 20 s at each time increment to allow scanning of the motion segment, which will affect the mechanical behavior of the specimen [28]. In addition, the maximum load that can be applied should be increased in order to make sure all specimens can be loaded until failure. With improvements, an experimental setup as proposed by Alkalay et al. [27] is promising for future applications.

In the current study, we applied an axial compression loading protocol, which represents a rather simple load pattern likely to be experienced by the spine during daily activities. Computational modeling has shown that in the metastatic spine axial compressive loading most heavily influences the risk of a burst fracture, which is commonly characterized by destruction of the posterior vertebral body cortex with the potential for retropulsion of bone or tumor fragments into the spinal canal [29]. Combined loading scenarios also demonstrated that axial loading is the principal factor contributing to burst fracture risk [29]. For these reasons, although representing a relatively simple load pattern, a uni-axial compression loading protocol is deemed appropriate.

The loading conditions of mechanical testing studies of human spines could be enhanced by using the full lumbar, thoracic, cervical, or even complete spine. Such specimens can be loaded using follower load techniques. As defined by Patwardhan et al., a follower load applies the compressive preload approximately tangential to the curve of the spine, passing through the centers of rotation of the spinal segments [30]. However, when such complex techniques are adopted, specimens are mostly subject to loads resembling more physiological movements [30-32], which are lower than the loads needed to induce failure. Moreover, one can argue that it becomes increasingly difficult to induce targeted failure of the vertebrae when using full lumbar, thoracic, cervical, or even complete spines. Hence, the experimental protocol described in this study should be regarded as a simplification of reality with an acceptable balance between realistic loading and predictability of the failure location of 3-segmental spinal units.

Conclusion

In conclusion, we developed an experimental setup and protocol able to induce targeted failure in 3-segment spinal units with intact posterior elements and able to capture the specimens' deformation in their post-failure state. In addition, this study illustrated the extreme importance of an adequate failure criterion for successful modeling of vertebral fractures in an experimental setup. Failure of the middle vertebral body in 3-segment spinal units cannot be assumed when using the clear (>10%) drop in force failure

criterion. In contrast, loading the specimens with at least 5 mm displacement increased the probability of inducing fractures in the target vertebrae. For testing of non-metastatic (control) vertebrae the failure location remains unpredictable, but the proposed method was able to successfully induce targeted failure in metastatically affected 3-segment spinal units. Preferably, the occurrence of failure should be confirmed post-testing.

Acknowledgments

We would like to thank Richard van Swam for his technical assistance and practical help with the experiments, the Department of Anatomy for providing the cadavers, and Willeke van Boekel-Geurts for her assistance with CT scanning.

References

1. Coleman RE. Skeletal complications of malignancy. *Cancer* 1997;80(8 Suppl):1588-1594.
2. Gralow J, Tripathy D. Managing metastatic bone pain: the role of bisphosphonates. *J Pain Symptom Manage* 2007;33(4):462-472.
3. Coleman RE. Metastatic bone disease: clinical features, pathophysiology and treatment strategies. *Cancer Treat Rev* 2001;27(3):165-176.
4. Costa L, Badia X, Chow E, Lipton A, Wardley A. Impact of skeletal complications on patients' quality of life, mobility, and functional independence. *Support Care Cancer* 2008;16(8):879-889.
5. Aquarius R, Homminga J, Verdonchot N, Tanck E. The fracture risk of adjacent vertebrae is increased by the changed loading direction after a wedge fracture. *Spine (Phila Pa 1976)* 2011;36(6):E408-412.
6. Buckley JM, Kuo CC, Cheng LC, Loo K, Motherway J, Slyfield C, Deviren V, Ames C. Relative strength of thoracic vertebrae in axial compression versus flexion. *Spine J* 2009;9(6):478-485.
7. Imai K. Analysis of vertebral bone strength, fracture pattern, and fracture location: a validation study using a computed tomography-based nonlinear finite element analysis. *Aging Dis* 2015;6(3):180-187.
8. Sahli F, Cuellar J, Perez A, Fields AJ, Campos M, Ramos-Grez J. Structural parameters determining the strength of the porcine vertebral body affected by tumours. *Comput Methods Biomech Biomed Engin* 2015;18(8):890-899.
9. Alkalay RN. Effect of the metastatic defect on the structural response and failure process of human vertebrae: an experimental study. *Clin Biomech (Bristol, Avon)* 2015;30(2):121-128.
10. Fang Z, Giambini H, Zeng H, Camp JJ, Dadsetan M, Robb RA, An KN, Yaszemski MJ, Lu L. Biomechanical evaluation of an injectable and biodegradable copolymer P(PF-co-CL) in a cadaveric vertebral body defect model. *Tissue Eng Part A* 2014;20(5-6):1096-1102.
11. Holub O, Lopez A, Borse V, Engqvist H, Kapur N, Hall RM, Persson C. Biomechanics of low-modulus and standard acrylic bone cements in simulated vertebroplasty: A human ex vivo study. *J Biomech* 2015;48(12):3258-3266.
12. McGowan DP, Hipp JA, Takeuchi T, White AA, 3rd, Hayes WC. Strength reductions from trabecular destruction within thoracic vertebrae. *J Spinal Disord* 1993;6(2):130-136.
13. Boger A, Heini P, Windolf M, Schneider E. Adjacent vertebral failure after vertebroplasty: a biomechanical study of low-modulus PMMA cement. *Eur Spine J* 2007;16(12):2118-2125.
14. Baum T, Grabeldinger M, Rath C, Garcia EG, Burgkart R, Patsch JM, Rummeny EJ, Link TM, Bauer JS. Trabecular bone structure analysis of the spine using clinical MDCT: can it predict vertebral bone strength? *J Bone Miner Metab* 2014;32(1):56-64.
15. Dimar JR, 2nd, Voor MJ, Zhang YM, Glassman SD. A human cadaver model for determination of pathologic fracture threshold resulting from tumorous destruction of the vertebral body. *Spine (Phila Pa 1976)* 1998;23(11):1209-1214.
16. Ebiara H, Ito M, Abumi K, Taneichi H, Kotani Y, Minami A, Kaneda K. A biomechanical analysis of metastatic vertebral collapse of the thoracic spine: a sheep model study. *Spine (Phila Pa 1976)* 2004;29(9):994-999.
17. Gaitanis IN, Carandang G, Phillips FM, Magovern B, Ghanayem AJ, Voronov LI, Havey RM, Zindrick MR, Hadjipavlou AG, Patwardhan AG. Restoring geometric and loading alignment of the thoracic spine with a vertebral compression fracture: effects of balloon (bone tamp) inflation and spinal extension. *Spine J* 2005;5(1):45-54.
18. Whealan KM, Kwak SD, Tedrow JR, Inoue K, Snyder BD. Noninvasive imaging predicts failure load of the spine with simulated osteolytic defects. *J Bone Joint Surg Am* 2000;82(9):1240-1251.
19. Windhagen HJ, Hipp JA, Silva MJ, Lipson SJ, Hayes WC. Predicting failure of thoracic vertebrae with simulated and actual metastatic defects. *Clin Orthop Relat Res* 1997(344):313-319.
20. Burklein D, Lochmuller E, Kuhn V, Grimm J, Barkmann R, Muller R, Eckstein F. Correlation of thoracic and lumbar vertebral failure loads with in situ vs. ex situ dual energy X-ray absorptiometry. *J Biomech* 2001;34(5):579-587.

21. Lu Y, Maquer G, Museyko O, Puschel K, Engelke K, Zysset P, Morlock M, Huber G. Finite element analyses of human vertebral bodies embedded in polymethylmethacrylate or loaded via the hyperelastic intervertebral disc models provide equivalent predictions of experimental strength. *J Biomech* 2014;47(10):2512-2516.
22. Algra PR, Heimans JJ, Valk J, Nauta JJ, Lachniet M, Van Kooten B. Do metastases in vertebrae begin in the body or the pedicles? Imaging study in 45 patients. *AJR Am J Roentgenol* 1992;158(6):1275-1279.
23. Shah AN, Pietrobon R, Richardson WJ, Myers BS. Patterns of tumor spread and risk of fracture and epidural impingement in metastatic vertebrae. *J Spinal Disord Tech* 2003;16(1):83-89.
24. Tschirhart CE, Nagpurkar A, Whyne CM. Effects of tumor location, shape and surface serration on burst fracture risk in the metastatic spine. *J Biomech* 2004;37(5):653-660.
25. Whyne CM, Hu SS, Lotz JC. Burst fracture in the metastatically involved spine: development, validation, and parametric analysis of a three-dimensional poroelastic finite-element model. *Spine (Phila Pa 1976)* 2003;28(7):652-660.
26. Whyne CM, Hu SS, Workman KL, Lotz JC. Biphasic material properties of lytic bone metastases. *Ann Biomed Eng* 2000;28(9):1154-1158.
27. Alkalay RN, Harrigan TP. Mechanical assessment of the effects of metastatic lytic defect on the structural response of human thoracolumbar spine. *J Orthop Res* 2016;34(10):1808-1819.
28. Adams MA, Dolan P. Time-dependent changes in the lumbar spine's resistance to bending. *Clin Biomech (Bristol, Avon)* 1996;11(4):194-200.
29. Tschirhart CE, Finkelstein JA, Whyne CM. Metastatic burst fracture risk assessment based on complex loading of the thoracic spine. *Ann Biomed Eng* 2006;34(3):494-505.
30. Patwardhan AG, Havey RM, Meade KP, Lee B, Dunlap B. A follower load increases the load-carrying capacity of the lumbar spine in compression. *Spine (Phila Pa 1976)* 1999;24(10):1003-1009.
31. Anderson DE, Mannen EM, Sis HL, Wong BM, Cadel ES, Friis EA, Boussein ML. Effects of follower load and rib cage on intervertebral disc pressure and sagittal plane curvature in static tests of cadaveric thoracic spines. *J Biomech* 2016;49(7):1078-1084.
32. Stanley SK, Ghanayem AJ, Voronov LI, Havey RM, Paxinos O, Carandang G, Zindrick MR, Patwardhan AG. Flexion-extension response of the thoracolumbar spine under compressive follower preload. *Spine (Phila Pa 1976)* 2004;29(22):E510-514.



5

Assessing spinal stability in metastatic bone disease: Comparing experimentally determined vertebral bone strength with predictions by experienced clinicians

Karlijn H.J. Groenen, Yvette M. van der Linden, Jacky W.J. de Rooy, André M.J. Sprengers,
Nico Verdonchot, Ronald H.M.A. Bartels, Allard J.F. Hosman, Esther Tanck.

BMC Musculoskeletal Disorders, submitted

Introduction

Patients with spinal bone metastases are at increased risk of developing pathological fractures and subsequent neurological injury. Such adverse events all dramatically affect the patients' quality of life and should, therefore, be prevented as much as possible [1-3]. Hence, accurate assessment of the fracture risk is required to prevent debilitating skeletal complications.

However, clinicians have difficulties in assessing fracture risk based on available diagnostic imaging data due to the absence of validated guidelines or an established predefined set of risk factors [4]. In order to assess whether newly developed guidelines improve upon clinical practice, current assessment skills of clinicians on fracture risk prediction should be determined.

In vitro loading experiments, in which cadaver vertebrae are loaded until failure, have been used to determine vertebral load to failure (i.e. bone strength) [5-7]. Comparing clinicians' estimates on bone strength with the experimentally determined bone strength, gives insight in the accuracy of current fracture risk prediction. Previous research on the femoral side has shown that the estimation of bone strength is not a trivial task [8, 9]. Potentially, clinicians may experience similar difficulties with the assessment of vertebral strength. This has never been tested before.

The optimal imaging modality to determine vertebral bone strength is neither known. In current clinical practice, different imaging modalities such as magnetic resonance imaging (MRI), computed tomography (CT) scans, and dual energy X-ray absorptiometry (DEXA) are used for diagnostic purposes.

In this study we assessed how accurate experienced clinicians are at predicting the strength of vertebrae with simulated metastatic lesions, as measured using *in vitro* biomechanical tests. In addition, we tested what imaging modality - MRI, CT, and/or DEXA - provides the best predictions.

Methods

In vitro loading experiment

Three complete spines free from deformities and malignancies were obtained from fresh frozen cadavers (2 men, 1 woman; age 80 - 92 years). The specimens were obtained from the Department of Anatomy with ethical approval authorized by the Dean of the Radboud university medical center's Medical Faculty and in accordance with the human cadaveric protocol. Each spine was sectioned into four 3-segment spinal units (T6-T8, T9-T11, T12-L2, and L3-L5) while carefully preserving the facet capsules, intervertebral discs, and spinal ligaments. In half of the specimens, we simulated metastatic lesions in the posterior half of the middle vertebral bodies. This location was selected with the

help of experienced clinicians. The relative size of the lesion was kept constant between specimens: the depth of the lesion comprised 75% of the maximal vertebral body width and its diameter 55% of the maximal vertebral body height. The resulting defect was filled with 0.5% solution of agarose gel formulated to mimic the average material properties of lytic tumor specimens [10, 11]. The removed core was dissected to isolate the cortical cap, which was reattached with polymethylmethacrylate (PMMA) to seal the lesion inside the vertebral body [10].

The upper and lower vertebrae of each specimen were embedded in PMMA before placing them in a hydraulic testing machine (MTS Systems Corporation, Eden Prairie, Minnesota, United States). The lower vertebra was constrained from translations and rotations in any direction. In contrast, free rotation in all directions was allowed for the upper vertebra. Preconditioning of the specimens consisted of cyclically, incrementally loading the specimens from 0 to 300 N, with 50 N increments. Following preconditioning, specimens were destructively tested in axial compression at 2 mm/min, while registering force and displacement of the plunger (100 Hz). Specimens were loaded for at least 5 mm. As soon as failure had occurred, the loading was paused.

Pre- and post-experiment CT (Aquilion/CXL, Toshiba Medical, Otawara, Japan; resolution 0.6 x 0.6 x 0.6 mm) scans were evaluated by an experienced radiologist to determine the occurrence of a fracture and/or collapse in one of the vertebral bodies. Experiments in which only the middle vertebra had failed were defined as successful. For the successful experiments, we determined the experimental load to failure from the force-displacement curves and used these specimens in the clinical assessment.

In addition, before experimentally testing the specimens DEXA scans, CT scans and MR images were acquired, which were used in the ranking assessment among clinicians (see Methods - Assessment by clinicians). Bone density of the L1-L4 region of each cadaver spine was measured in a water basin using DEXA (Discovery DXA system, Hologic, Inc., Marlborough, Massachusetts, United States). For the CT scans, the specimens were scanned in a water basin (Brilliance Big Bore, Philips, Eindhoven, The Netherlands; resolution 1.0 x 1.0 x 1.0 mm). Regarding MRI scanning, fat-saturated VIBE T1 weighted images and T2 weighted restore pulse images were obtained with an image voxel size of 1.0 x 1.0 x 1.0 mm (TrioTim, Siemens Healthcare, Erlangen, Germany).

Assessment by clinicians

Radiological examination of the pre- and post-experiment CT scans revealed that nine out of 12 experiments were successful and, hence, used in the clinical assessment (Table 1). Four clinicians experienced in treating patients with metastatic spinal disease (orthopedic surgeon with spinal interest, neurosurgeon with spinal interest, radiation oncologist, and radiologist) were asked to rank the middle vertebrae on bone strength from weak to strong. We did not prescribe any rules or guidelines for ranking. This

ranking was performed in two sessions (A, B) of three consecutive rounds, with different sequences of imaging modalities provided in each round:

- A1. MRI;
- A2. MRI + CT;
- A3. MRI + CT + DEXA;
- B1. CT;
- B2. CT + MRI;
- B3. CT + MRI + DEXA.

DEXA results included the T-score and the corresponding clinical interpretation (normal, osteoporotic, osteopenic). Additional information on the patients' gender, age, length and body weight, and on the mechanical test was provided (Table 1). Images were provided using a custom made digital survey in Cirrus, a scoring and viewing platform produced in-house by Radboud university medical center based on MeVisLab (MeVisLab, MeVis Medical Solutions AG). To avoid recognition of specimens, time between sessions A and B was at least seven weeks for all observers, the observers were not notified about their performance in session A, and the order in which specimens were displayed in session B was rearranged. Furthermore, the clinicians were asked to indicate what provided information (CT, MRI, DEXA or gender and age) was most important for them to rank the specimens.

Table 1 Information on the specimens provided to the clinicians during the ranking rounds. T-score and bone quality were only provided in sessions A3 and B3. Note: The experiments using specimen b2, c1, and c4 were not successful and, hence, not used in the clinical assessment.

Sex (M/F)	Age at death [y]	Weight [kg]	Length [cm]	BMI [kg/m ²]	T- score	Bone quality	Specimen		Lesion (L) / Control (C)
F	80	44	157	17.9	-3.3	osteoporotic	a1	T6-T8	C
							a2	T9-T11	L
							a3	T12-L2	L
							a4	L3-L5	C
M	92	87	187	24.9	-0.7	normal	b1	T6-T8	L
							b2	T9-T11	C
							b3	T12-L2	C
							b4	L3-L5	L
M	80	55	163	20.7	-3.1	osteoporotic	c1	T6-T8	C
							c2	T9-T11	L
							c3	T12-L2	L
							c4	L3-L5	C

Analysis of data

We ranked the vertebrae on experimental load to failure, the weakest specimen receiving rank number one. The rankings by the clinicians were compared to the experimental ranking using Kendall's tau correlation coefficient (τ), which defines the degree of similarity between two rankings ($\tau = 1$ indicates perfect agreement; $\tau = -1$

indicates total disagreement; $\tau = 0$ indicates that the variables are independent) [12]. Comparisons were made for all rounds of ranking to evaluate what information enabled the most accurate ranking. Inter-observer agreement in similar ranking rounds was calculated using τ . Statistical analyses were performed in SPSS v22 (SPSS Inc., Chicago, Illinois, United States). Results were considered statistically significant if $p < 0.05$. In addition, the information perceived by the clinicians as most important for ranking the specimens was assigned four points, while the least important information received one point. The scores per factor were then summed for all clinicians.

Results

Accuracy of vertebral strength prediction

There were considerable differences in the correspondence between the predicted and experimental rankings between observers, ranging from weak to reasonably well. For the MRI, MRI + CT, and MRI + CT + DEXA rounds τ ranges were 0.278 ($p = 0.297$) to 0.556 ($p < 0.05$), 0.333 ($p = 0.211$) to 0.722 ($p < 0.01$), and 0.333 ($p = 0.211$) to 0.667 ($p < 0.05$), respectively (Figure 1). For the CT, CT + MRI, and CT + MRI + DEXA rounds τ ranges were 0.111 ($p = 0.677$) to 0.611 ($p < 0.05$), 0.278 ($p = 0.297$) to 0.556 ($p < 0.05$) and 0.278 ($p = 0.297$) to 0.778 ($p < 0.01$), respectively (Figure 1). Overall, the clinicians ranked the vertebrae in higher agreement with the experimental results in session A starting with MRI, than in session B starting with CT. In addition, the current results illustrated little consistency in ranking performance between sessions A and B. Clinicians who obtained a relatively good correlation between predicted and experimental ranking in session A, not necessarily obtained similar results in session B (observers A and C). Also, clinicians who performed relatively poor in session A, showed improved correlations in session B (observer D). Only one clinician (observer B) performed relatively consistent in all ranking rounds, but still not optimal (Figure 1).

Optimal imaging modality

When considering ranking session A, providing the clinicians with only MRI scans resulted in the lowest correlation between the observed and experimental rankings for all clinicians (Figure 1). Adding CT scans increased the correlation considerably for all observers, whereas including DEXA information hardly changed the correlation. In contrast, these trends could not be seen in session B. When adding MRI to CT scans, one clinician performed clearly better (observer B), one clinician performed worse (observer A), and two clinicians performed comparably in both rounds (observers C and D). When additional DEXA scans were provided, only one clinician obtained a considerably higher

correlation with the experimental results (observer B), whereas the other three observers' performance remained the same.

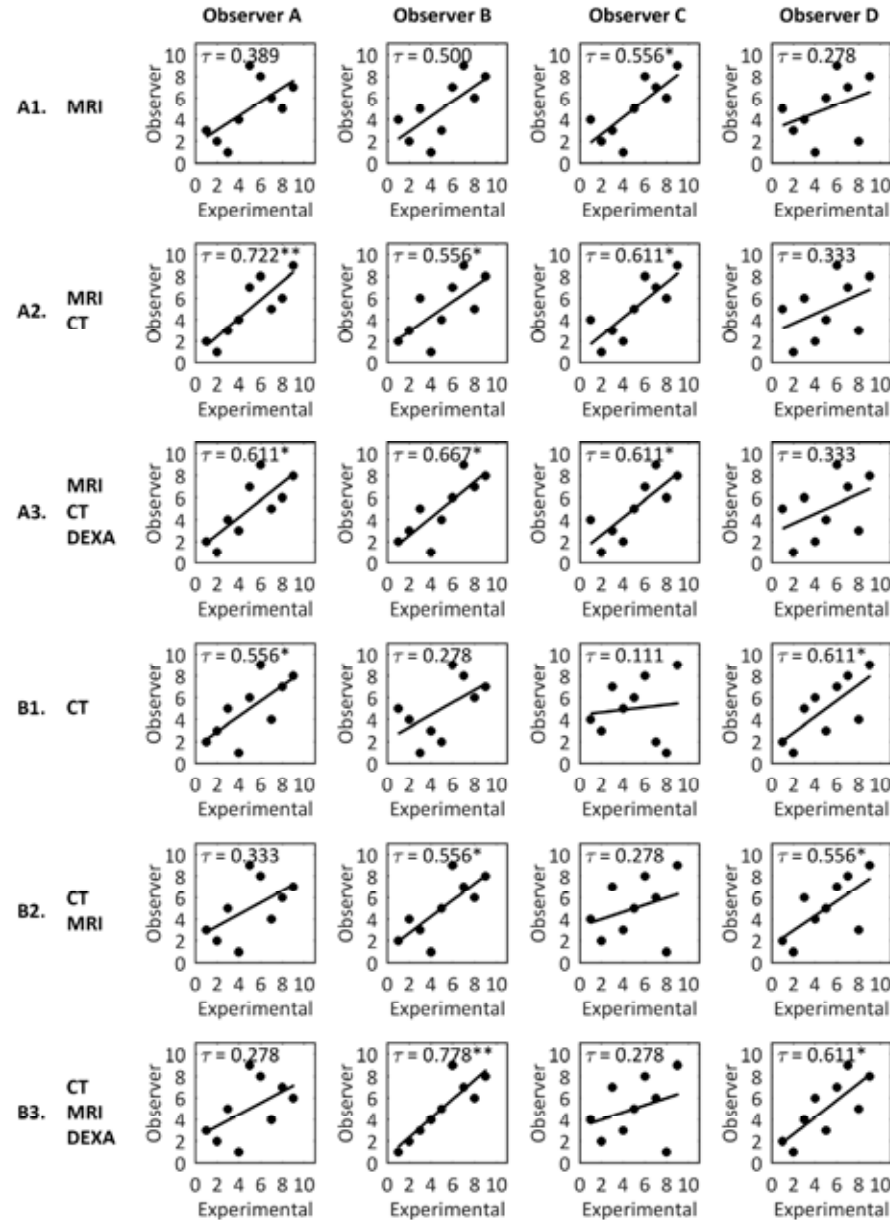


Figure 1 Kendall's tau correlation coefficients (τ) between the experimental and predicted rankings on vertebral strength for all ranking rounds (A1, A2, A3, B1, B2, B3) and all clinicians (A, B, C, D). * and ** indicate significance at the 0.05 and 0.01 level, respectively.

Furthermore, clinicians indicated that, of the provided input information, CT scans were considered to be most important for the prediction of vertebral strength (Figure 2). Gender and age, as clinical predictors for bone strength, were reported as least useful.

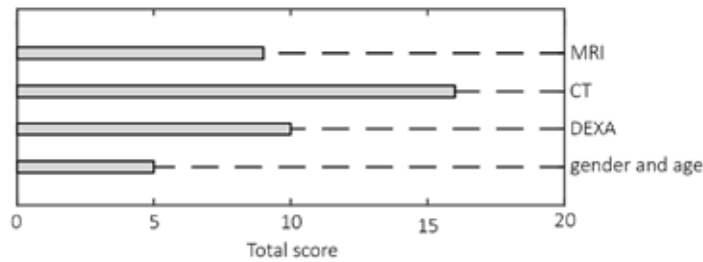


Figure 2 Which of the following information is in your opinion most important for ranking the specimens on vertebral bone strength?
Chart showing the results of a survey on clinicians’ strategies for assessing vertebral strength. Four points were assigned to the most important factor, while the least important factor received one point. The scores per factor were then summed for all clinicians.

Inter-observer agreement

The Kendall’s tau correlation coefficients among clinicians were highly variable and ranged from poor ($\tau = -0.167$, ($p = 0.532$) to substantial ($\tau = 0.722$, $p < 0.01$) (Table 2). The inter-observer agreement seemed to not be affected by the imaging modality provided. In addition, we could not identify any pair of clinicians that consistently agreed with each other. While observers B and C, for example, showed the highest inter-observer agreement in session A, they no longer did in session B.

Discussion

This study assessed the accuracy of ratings of vertebral strength by experienced clinicians in an experimental setup and tested what imaging modality - MRI, CT, and/or DEXA - provides the best predictions.

The large variations in the correlations between the predicted and experimental rankings might be explained by the absence of clear clinical guidelines. Consequently, clinicians possibly use their own experience and strategies and rely on different determinants to assess vertebral strength. Not only did we observe large variations between clinicians, we also saw that clinicians performed inconsistently in repeated ranking tasks, even though they had the same input at their disposal. This indicates that the clinicians used varying strategies over time for estimating vertebral bone strength. Hence, although fracture risk estimation is only one of the parameters to decide which

treatment is best for a patient, the high variability in fracture risk assessment as found in this study is likely to introduce variation in patient treatment in clinical reality.

Furthermore, based on only session A, we could not conclude whether the optimal medical imaging modality requires both MRI and CT, or whether CT only also suffices. Interestingly, the raters unanimously indicated CT scans to be most important for vertebral strength predictions. However, this was not reflected in their performance on the ranking tasks. When only CT scans were provided, most clinicians performed worse than in round A2 (MRI+CT). However, the correspondence between experimental and predicted vertebral strength was very different over sessions A and B, both within and between clinicians. As DEXA scans did not seem to have added value and ranking performance using CT and/or MRI highly varied, the current study did not provide conclusive evidence about the optimal imaging modality.

Table 2 Inter-observer agreement (t) per ranking round.

Ranking round	Provided imaging		Observer A	Observer B	Observer C
A1	MRI	Observer B	0.222		
		Observer C	0.500	0.722**	
		Observer D	0.444	0.444	0.722**
A2	MRI + CT	Observer B	0.389		
		Observer C	0.667*	0.611*	
		Observer D	0.500	0.556*	0.611*
A3	MRI + CT + DEXA	Observer B	0.389		
		Observer C	0.556*	0.722**	
		Observer D	0.611*	0.444	0.500
B1	CT	Observer B	0.389		
		Observer C	0.222	-0.167	
		Observer D	0.278	0.333	0.389
B2	CT + MRI	Observer B	0.556*		
		Observer C	0.389	0.389	
		Observer D	0.333	0.444	0.722**
B3	CT + MRI + DEXA	Observer B	0.389		
		Observer C	0.333	0.389	
		Observer D	0.111	0.611*	0.444

* Correlation is significant at the 0.05 level (2-tailed)

** Correlation is significant at the 0.01 level (2-tailed)

Vertebral bone strength is determined by a complex interplay of various factors. Therefore, it might be difficult to comprehend and hard to capture in a set of simple guidelines. The current results show the urgent need for a more objective, sophisticated tool that can take into account all multi-factorial aspects. Finite element (FE) analysis is an advanced computer technique of structural stress analysis developed in engineering

mechanics and has found applications in bone mechanics, using so-called patient-specific FE models. Patient-specific FE models are based on (quantitative) CT scans, from which the bone's geometry and mechanical behavior can be extracted [8, 13-16]. Therefore, such a model does not only accommodate parameters related to lesion and patient, but also covers additional aspects that play an important role in the assessment of the risk of fracture, such as the initial strength of the bone and the daily loads on the bone. In fact, previous studies have already shown that FE computer models are indeed able to accurately predict failure behavior of bones [17-20] and are able to improve the strength prediction of metastatic femora compared with the prediction by experienced clinicians [8, 19]. Although improvements in terms of automation, user-friendliness, and computational time are required, we feel that this method has a promising clinical application in spinal metastases as well.

Our study has some limitations. The simplified laboratory conditions, the simulated lytic metastases, and the cadaver CT and MRI scans might have been different from those seen in clinical practice. However, we provided the clinicians with ample explanation about the experimental setup and used a simple loading configuration. The geometrical appearance of the lesions was simplified as compared to bone metastases in actual patients. If these simplified conditions were difficult for the clinicians to imagine, they might have even more difficulty in predicting the risk of fracture *in vivo*. Some observers mentioned that the quality of the scans was suboptimal. Although the CT and MR images provided were cadaver scans of 3-segment spinal units, we used clinical settings. In addition, an experienced musculoskeletal radiologist confirmed that the image quality was comparable to the clinical standard. Therefore, we feel that the use of cadaver scans has not affected the clinicians' ranking performances. In contrast, the fact that the patient's clinical situation could not be taken into account in this *in vitro* study might have affected the rating strategies used. In a clinical setting, the presence or absence of pain is often used as a major indicator of spinal instability and is, therefore, possibly a sign of reduced vertebral strength.

In the current study four clinicians performed the ranking tasks independently. However, in clinical practice multidisciplinary consultation meetings are more frequently organized. In these multidisciplinary meetings clinicians with different expertise closely collaborate to reach consensus on patient diagnosis or treatment. Repeating the ranking tasks in a panel would reflect ideal clinical settings and would give insight in whether a joint decision would result in an improved strength prediction.

Moreover, it should be emphasized that the eventual aim is to improve the care of patients presenting with vertebral metastatic lesions. Our study focused on estimating the remaining vertebral strength. In case of improved fracture risk prediction, treatment decisions to e.g. irradiate for pain reduction or perform surgical interventions to preserve or restore spinal stability could be made more adequate. However, treatment decision making in clinical practice is a rather complex process, which does not solitary

depend on estimating bone strength: factors such as the patients' estimated life expectancy and clinical performance should also be taken into account.

In conclusion, this simulation-study showed considerable differences in the clinicians' predictions compared to the experimental assessment of bone strength in vertebrae: agreement ranged from weak to reasonably well. Moreover, inter-observer agreement was highly variable. In addition, as ranking of the vertebrae showed large variations in relation to imaging modality, the current study did not provide conclusive evidence about the optimal imaging modality. The results found in the current study reflect an urgent need for a more objective protocol or method to assess vertebral strength.

Acknowledgments

We would like to thank Richard van Swam for his technical assistance and practical help with the experiments, the Department of Anatomy for providing the cadavers, Willeke van Boekel-Geurts and Peter van Kollenburg for their assistance with CT and MRI scanning, Marga Ouwens and Merijn Janssen for making the DEXA scans, and Sven Lafebre for his help with developing and programming the digital survey.

References

1. Bakar D, Tanenbaum JE, Phan K, Alentado VJ, Steinmetz MP, Benzel EC, Mroz TE. Decompression surgery for spinal metastases: a systematic review. *Neurosurg Focus* 2016;41(2):E2.
2. Harel R, Angelov L. Spine metastases: current treatments and future directions. *Eur J Cancer* 2010;46(15):2696-2707.
3. Sutcliffe P, Connock M, Shyangdan D, Court R, Kandala NB, Clarke A. A systematic review of evidence on malignant spinal metastases: natural history and technologies for identifying patients at high risk of vertebral fracture and spinal cord compression. *Health Technol Assess* 2013;17(42):1-274.
4. Fisher CG, DiPaola CP, Ryken TC, Bilsky MH, Shaffrey CI, Berven SH, Harrop JS, Fehlings MG, Boriani S, Chou D, Schmidt MH, Polly DW, Biagini R, Burch S, Dekutoski MB, Ganju A, Gerszten PC, Gokaslan ZL, Groff MW, Liebsch NJ, Mendel E, Okuno SH, Patel S, Rhines LD, Rose PS, Sciubba DM, Sundaresan N, Tomita K, Varga PP, Vialle LR, Vrionis FD, Yamada Y, Fourney DR. A novel classification system for spinal instability in neoplastic disease: an evidence-based approach and expert consensus from the Spine Oncology Study Group. *Spine (Phila Pa 1976)* 2010;35(22):E1221-1229.
5. Alkalay RN. Effect of the metastatic defect on the structural response and failure process of human vertebrae: an experimental study. *Clin Biomech (Bristol, Avon)* 2015;30(2):121-128.
6. Buckley JM, Kuo CC, Cheng LC, Loo K, Motherway J, Slyfield C, Deviren V, Ames C. Relative strength of thoracic vertebrae in axial compression versus flexion. *Spine J* 2009;9(6):478-485.
7. Burklein D, Lochmuller E, Kuhn V, Grimm J, Barkmann R, Muller R, Eckstein F. Correlation of thoracic and lumbar vertebral failure loads with in situ vs. ex situ dual energy X-ray absorptiometry. *J Biomech* 2001;34(5):579-587.
8. Derikx LC, van Aken JB, Janssen D, Snyers A, van der Linden YM, Verdonschot N, Tanck E. The assessment of the risk of fracture in femora with metastatic lesions: comparing case-specific finite element analyses with predictions by clinical experts. *J Bone Joint Surg Br* 2012;94(8):1135-1142.
9. Hipp JA, Springfield DS, Hayes WC. Predicting pathologic fracture risk in the management of metastatic bone defects. *Clin Orthop Relat Res* 1995(312):120-135.
10. Whyne CM, Hu SS, Lotz JC. Burst fracture in the metastatically involved spine: development, validation, and parametric analysis of a three-dimensional poroelastic finite-element model. *Spine (Phila Pa 1976)* 2003;28(7):652-660.
11. Whyne CM, Hu SS, Workman KL, Lotz JC. Biphasic material properties of lytic bone metastases. *Ann Biomed Eng* 2000;28(9):1154-1158.
12. Abdi H. The Kendall Rank Correlation. In: Salkind NJ, ed. *Encyclopedia of Measurement and Statistics*. Thousand Oaks: Sage 2007:508-510.
13. Homminga J, Aquarius R, Bultink VE, Jansen CT, Verdonschot N. Can vertebral density changes be explained by intervertebral disc degeneration? *Med Eng Phys* 2012;34(4):453-458.
14. Jones AC, Wilcox RK. Finite element analysis of the spine: towards a framework of verification, validation and sensitivity analysis. *Med Eng Phys* 2008;30(10):1287-1304.
15. Lenaerts L, van Lenthe GH. Multi-level patient-specific modelling of the proximal femur. A promising tool to quantify the effect of osteoporosis treatment. *Philos Trans A Math Phys Eng Sci* 2009;367(1895):2079-2093.
16. Knowles NK, Reeves JM, Ferreira LM. Quantitative Computed Tomography (QCT) derived Bone Mineral Density (BMD) in finite element studies: a review of the literature. *J Exp Orthop* 2016;3(1):36.
17. Crawford RP, Cann CE, Keaveny TM. Finite element models predict in vitro vertebral body compressive strength better than quantitative computed tomography. *Bone* 2003;33(4):744-750.
18. Imai K. Analysis of vertebral bone strength, fracture pattern, and fracture location: a validation study using a computed tomography-based nonlinear finite element analysis. *Aging Dis* 2015;6(3):180-187.
19. Tanck E, van Aken JB, van der Linden YM, Schreuder HW, Binkowski M, Huizenga H, Verdonschot N. Pathological fracture prediction in patients with metastatic lesions can be improved with quantitative computed tomography based computer models. *Bone* 2009;45(4):777-783.
20. Zysset PK, Dall'ara E, Varga P, Pahr DH. Finite element analysis for prediction of bone strength. *Bonekey Rep* 2013;2:386.



6

Case-specific non-linear finite element models to predict failure behavior in 3-segment spinal units

Karlijn H.J. Groenen, Thom Bitter, Tristia C.G. van Veluwen, Yvette M. van der Linden,
Nico Verdonshot, Esther Tanck, Dennis Janssen.

Journal of Orthopaedic Research, under review

Introduction

Patients with cancer and spinal bone metastases are at risk of developing pathological fractures and subsequent pain and neurological complications [1, 2]. Hence, preventing pathological fractures is important to preserve quality of life and prevent debilitating complications [3, 4].

Quantitative computed tomography (QCT)-based finite element (FE) models are a promising tool for fracture risk assessment. These models can not only accommodate parameters related to the lesion, but can also cover additional aspects that play an important role in the assessment of the risk of fracture, such as the bone geometry, bone quality, and the daily loads applied to the bone [5]. Prior studies demonstrated that QCT-based FE models can provide accurate predictions of vertebral stiffness and strength, when compared to *in vitro* experiments [6-11].

Most FE models predicting vertebral failure behavior are confined to single vertebrae [6-11]. However, the simplified loading conditions applied to single vertebrae are bound to introduce loading artifacts and may, therefore, be of less clinical relevance. A more physiological loading condition can be obtained by using 3-segment spinal units, consisting of three consecutive vertebrae and two intervertebral discs. This way, the middle vertebra is loaded via two intervertebral discs, the posterior elements, and the spinal ligaments; thereby transferring load as would happen under *in vivo* conditions. Using 3-segment spinal units, however, makes *in vitro* experiments and simulations more complex. This complexity is obviously one of the reasons why vertebral strength has not yet been predicted using FE models of 3-segment spinal units.

In addition, the mathematical relationships between bone density characteristics and material properties (hereinafter referred to as *material model*) describing bone behavior may have a significant effect on the FE predictions. We previously demonstrated that FE models of metastatic femurs can accurately predict both load to failure ($R^2 = 0.93$, $p < 0.001$) and fracture location, and can improve upon the strength prediction compared with experienced clinicians [12, 13]. The material model of Keyak et al. [14] was used in these simulations and includes post-yield plastic behavior. Adopting material models based on vertebral bone might more accurately predict vertebral failure behavior. However, vertebral material models reported in literature only partly describe mechanical behavior, e.g. limiting to linking bone density to Young's modulus and/ or yield stress, disregarding post-yield behavior [15-21]. In addition, these material models have been based on a broad range of bone densities. The resulting Young's moduli or yield stresses also vary considerably for a particular bone density.

The goal of this study was to develop a more clinically relevant, case-specific non-linear FE model of 3-segment spinal units able to predict failure behavior. When testing 3-segment spinal units it is not trivial that the vertebrae that failed during the *in vitro* experiments are correctly indicated by the FE models. Therefore, we firstly determined whether the FE models were able to correctly indicate which vertebrae failed during the

experiments. Secondly, we investigated whether the deformation of the specimens was predicted correctly. Finally, we assessed whether the FE models were able to predict stiffness and load to failure. We furthermore studied the effects of different material models on the prediction of failure behavior by applying material models representing the broad spectrum reported in literature [14-18]. The overall aim of our project is to improve the clinical assessment of fracture risk in spinal metastatic bone disease.

Methods

The *in vitro* testing methodology, previously detailed [22], is hereby described in brief.

Specimen preparation

Three complete spines free from deformities and malignancies were obtained from fresh frozen cadavers (2 men, 1 woman; aged 80 - 92 years). The specimens were obtained from the Department of Anatomy with ethical approval authorized by the Dean of the Radboud university medical center's Medical Faculty and in accordance with the human cadaveric protocol. Each spine was sectioned into four 3-segment spinal units (T6-T8, T9-T11, T12-L2, and L3-L5) while carefully preserving the facet capsules, intervertebral discs, and spinal ligaments. Since the ultimate goal of our project is to predict vertebral failure in spinal metastatic bone disease, we simulated metastatic lesions in the middle vertebral bodies in half of the specimens. The relative size of the lesion was kept constant between specimens: the depth of the lesion comprised 75% of the maximal vertebral body width and its diameter 55% of the maximal vertebral body height. The resulting defect was filled with 0.5% solution of agarose gel formulated to mimic the average material properties of lytic tumor specimens [23, 24]. The removed core was dissected to isolate the cortical cap, which was reattached with polymethylmethacrylate (PMMA) to seal the lesion inside the vertebral body [23]. The upper and lower vertebrae of each specimen were embedded in PMMA.

The specimens were subsequently immersed in water and scanned using QCT (Brilliance Big Bore, Philips Healthcare, Best, The Netherlands; 120 kVp, 300 mAs, slice thickness 1.0 mm, pitch 0.938, standard reconstruction, in plane resolution 0.977 mm). A solid calibration phantom (0, 50, 100, and 200 mg/ml calcium hydroxyapatite; Image Analysis, Columbia, Kentucky, United States) was scanned alongside. Bone density of the L1-L4 region of each specimen was measured in water using dual-energy X-ray absorptiometry (DEXA) (Discovery DXA system, Hologic, Inc., Marlborough, Massachusetts, United States). After QCT and DEXA scanning, four and five tantalum pellets were inserted into the upper (spinous process and the left, right, and anterior wall of the vertebral body) and lower vertebrae (left and right transverse processes and

the left, right, and anterior wall of the vertebral body), respectively, to allow for Rontgen Stereophotogrammetric Analysis (RSA).

Mechanical experiment

The specimens were fixated in a custom-made testing jig inside an MTS machine (MTS Systems Corporation, Eden Prairie, Minnesota, United States). The lower vertebra was constrained from translations and rotations in any direction. Free rotation in all directions was allowed for the upper vertebra. Following preconditioning, specimens were destructively tested in axial compression at 2 mm/min, while registering force and displacement (100 Hz). Specimens were loaded for at least 5 mm. RSA photographs were taken every 15 seconds to calculate the three-dimensional (3D) position of the tantalum markers. To facilitate fracture detection and to capture the specimens' post-failure state, the specimens were fixated by embedding them in PMMA that was contained by a plastic bag, while the specimens were in the final loading position. Pre- and post-experiment CT (Aquilion/CXL, Toshiba Medical, Otawara, Japan; resolution 0.6 x 0.6 x 0.6 mm) scans were evaluated by an experienced radiologist to determine the occurrence of a fracture and/or collapse in one of the vertebral bodies. Subsequently, we determined the load to failure from the force-displacement curves. The displacement in the loading direction of the upper vertebrae with respect to the lower vertebrae was calculated using the 3D positions of the tantalum markers, in order to account for play in the experimental setup. Force-RSA displacement curves were generated to determine the experimental stiffness.

Finite element model

Based on QCT data we constructed FE models of all 3-segment spinal units. Geometric information for the vertebral bones and intervertebral discs (IVDs) was retrieved by segmenting the QCT images (Materialise Mimics 14.0, Materialise NV, Leuven, Belgium). The IVD was discretized into a nucleus pulposus (NP) and annulus fibrosis (AF), with the NP area constituting approximately 40% of the total disc area [25, 26]. All structures were meshed using four-noded tetrahedral elements (mean edge length 2 mm) (HyperMesh 2017.1, HyperWorks, Altair Engineering, Inc. Troy, Michigan, United States). Subsequently, the Herrmann formulation was applied to disc elements to account for the discs being nearly incompressible. Touching contact without friction between facet joints was employed. The positions of the tantalum markers inserted into the vertebrae were copied to the FE model.

Within the IVD, the NP and AF were modeled using hyperelastic Mooney-Rivlin material models. The AF was furthermore modeled as a composite material with embedded rebar elements to represent the collagen fiber reinforcement. The fibers were placed circumferentially at $\pm 20^\circ$ with the transversal plane and only acted in

tension. The mechanical properties of the NP and AF used in previous FE studies vary greatly [25, 27, 28]. The properties used in the current model are described in Table 1.

Table 1 Material properties used for the intervertebral discs.

		C10	C01	Bulk modulus [MPa]	E [MPa]	ν
Nucleus		0.2	0.045	$1.0 \cdot 10^6$		
Annulus fibrosis	Ground substance	0.21	0.045	$1.2 \cdot 10^6$		
	Fibers				650	0.33

To allow for bone heterogeneity, ash density (ρ_{ash}) of each element was determined from the QCT data using linear calibration [14]. Subsequently, isotropic non-linear material properties were assigned to each element based on four different Young's modulus-density and yield stress-density relationships previously empirically determined: (1) Keyak et al. [14]; (2) Kopperdahl et al. [15]; (3) Morgan et al. [16, 17]; and (4) Ouyang et al. [18]. For Ouyang's material model, we modeled the Young's modulus both without (4a) and with (4b) the strain rate factor, which is often discarded in quasi-static simulation studies [29]. While the material model described by Keyak et al. is based on femoral bone, the others are based on vertebral bone. The vertebral material models were chosen as representatives for the high variations in both the bone densities used to define the material models and the resulting Young's modulus or yield stress [30]. Most material models were based on apparent density (ρ_{app}) or wet density (ρ_{wet}) rather than on ρ_{ash} . For these cases, ρ_{app} and ρ_{wet} were converted into ρ_{ash} using $\rho_{ash} = 0.551 \rho_{app}$ and $\rho_{ash} = 0.551 \rho_{wet}$, respectively [30-32]. Moreover, only the material model reported by Keyak et al. included post-yield plastic behavior. Hence, when studying the impact of the chosen material model, the Young's modulus and the yield stress were obtained from the varying material models, and post-yield behavior as described by Keyak et al. was implemented in all models. In order to achieve continuous post-failure behavior, the initial perfectly plastic phase, strain softening phase, and indefinite perfectly plastic phase were scaled according to the yield stress (Table 2).

The experimental boundary conditions were mimicked as realistically as possible in the FE simulations (Figure 1). In the FE simulations we used a displacement-controlled loading condition (0.1 mm/increment). The load was applied on a node that matched the point of load application during the experiments (load node). This node was connected to the upper vertebra via rigid links. The FE simulations were performed with MSC Marc (MSC.MARC2013r1; MSC Software Corporation, Santa Ana, California, United States). The incremental displacement in the loading direction of the upper vertebra with respect to the lower vertebra was registered via the virtual RSA markers in the upper and lower vertebrae. The total reaction force in the loading direction was defined as reaction force in the load node due to the prescribed displacement. Structural fracture was assumed to occur when the total reaction force exhibited a drop in force. Stiffness was determined from the reaction force-RSA based displacement curve. The location of

failure was defined by elements that plastically deformed [14] when the load to failure was reached.

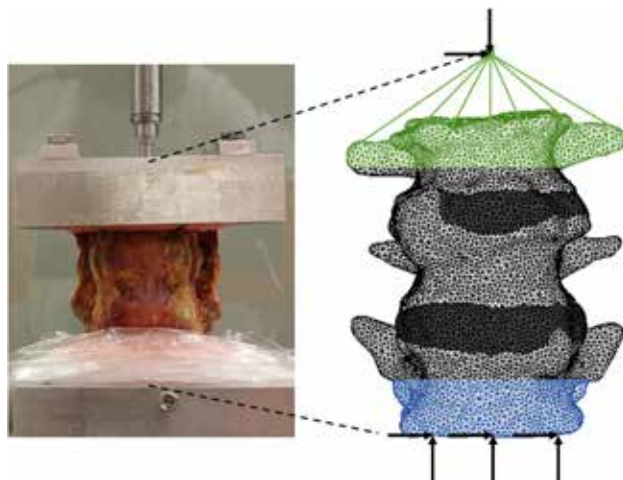


Figure 1 Diagrams showing the experimental setup (left) and the same conditions mimicked in the FE models (right). The displacement applied to the FE model was applied to the load node. The load node was constrained from translations in the horizontal plane. All surface nodes in the green colored area were connected to the load node using rigid links. The surface nodes in the blue colored area were constrained from translations and rotations in any direction.

For a more detailed analysis of fracture location, we assessed the experimentally determined and FE predicted 3D deformation of the specimens. To this end, contours of the vertebrae post-experiment and post-FE were qualitatively examined with respect to pre-experimental vertebral contours. Contours were obtained from stereolithography (stl) files obtained from segmentations of the pre- and post-experimental CT scans, and the FE model in the post-failure state. The iterative closest point (ICP) method was used to register stl files based on the lower vertebrae.

Data analysis

Specimens in which multiple vertebrae failed during the experiments were excluded from further analyses, since our experimental test setup did not allow for assessing the order of vertebral failure. The vertebrae within the 3-segment spinal units that failed in the FE simulations and corresponding experiments were qualitatively compared. In addition, the deformation of the experimental specimens was qualitatively compared to the deformation predicted by the FE models. In case fracture was predicted to occur in the incorrect vertebra, the corresponding simulation was excluded from stiffness and load to failure analyses. We used linear regression analysis to evaluate relations between the predicted and measured stiffness and load to failure. Statistical analyses were performed in MATLAB (Release 2016b, The Mathworks, Inc., Natick, Massachusetts, United States). Results were considered significant if $p < 0.05$.

Table 2 Bone material models implemented in the finite element models.

	Young's Modulus (original)	Yield stress (original)	Young's Modulus (ρ_{ash})	Yield stress (ρ_{ash})	Scaling factor for post failure behavior
1	E = 14900 $\rho_{ash}^{1.86}$	S = 102 $\rho_{ash}^{1.80}$	E = 14900 $\rho_{ash}^{1.86}$	S = 102 $\rho_{ash}^{1.80}$	-
2	E = 2580 $\rho_{wet}^{1.34}$	S = 23.2 $\rho_{wet}^{1.60}$	E = 5734 $\rho_{ash}^{1.34}$	S = 60.21 $\rho_{ash}^{1.60}$	X = 0.746 $\rho_{ash}^{-0.1112}$
3	E = 4730 $\rho_{app}^{1.56}$	S = 37.1 $\rho_{app}^{1.74}$	E = 11986 $\rho_{ash}^{1.56}$	S = 104.66 $\rho_{ash}^{1.74}$	X = 1.014 $\rho_{ash}^{-0.0334}$
4a (Excluding strain rate factor)	E = 2383 $\rho_{app}^{1.88}$	S = 7.5 $\rho_{app}^{1.29}$	E = 7307 $\rho_{ash}^{1.88}$	S = 16.18 $\rho_{ash}^{1.29}$	X = 0.360 $\rho_{ash}^{-0.2834}$
4b (Including strain rate factor $\dot{\epsilon}$)	E = 2383 $\rho_{app}^{1.88} \epsilon^{0.07}$	S = 7.5 $\rho_{app}^{1.29}$	E = 7307 $\rho_{ash}^{1.88} \epsilon^{0.07}$	S = 16.18 $\rho_{ash}^{1.29}$	X = 0.360 $\rho_{ash}^{-0.2834}$

$\dot{\epsilon}$ was assumed to be $1 \cdot 10^{-4} s^{-1}$

Results

In vitro experiments

Data from all specimens and experimental results are summarized in Table 3. Radiological examination of the pre- and post-experimental CT scans showed that 11 specimens failed in only one vertebra and were included for further analyses. Of these, ten specimens fractured in the middle vertebrae, whereas one fractured in the lower vertebra (B2).

FE Simulations

The 11 experiments in which one vertebra failed were all simulated by the FE models. For each specimen we ran five simulations comprising the different material models, resulting in 55 simulations. One simulation had convergence problems before reaching failure (Kopperdahl et al.: specimen B3). However, the force-displacement curve already started to deflect. Therefore, this simulation was included in the load to failure analysis.

Identification of the vertebra to fail

The material model implemented did not affect which vertebra was predicted to fail (i.e. which vertebra was identified as weakest). Furthermore, in 10 out of 11 specimens the vertebra to fail was correctly indicated by the FE model (Figure 2). This was not necessarily the middle vertebra, since in specimen B2 both the experiment and FE simulations indicated the lower vertebra as the weakest one. Whereas in specimen A4 the middle vertebra failed during the experiment, the lower one was predicted to fail by the FE simulations. Consequently, specimen A4 was dismissed from further analyses.

Specimen deformation

When comparing the measured experimental deformation to the deformation predicted by the FE models, it appeared that most models did not converge to a point where the full experimental displacement was reached, as shown by the difference between the post-experimental and predicted position of the upper vertebra (Figure 3). Furthermore, in case deformation barely occurred in the lower vertebra, this was predicted correctly by the FE models: the contours of the pre- and post-experimental segmentations as well as of the FE model were overlapping. While in the experiments often substantial fractures were seen in the endplates, this was not observed to such a large extent in the simulations, where plasticity mainly occurred transversally in the vertebral bodies (Figure 2). In addition, the material model did not majorly affect the predicted plasticity pattern.

Table 3 Overview of the tested specimens and experimental results.

Sex (M/F)	Age at death [y]	Weight [kg]	Length [cm]	BMI [kg/m ²]	T- score	Bone quality	Specimen	Lesion (L) / Intact (I)	Failed vertebra(e) Upper (U) Middle (M) Lower (L)	Stiffness [N/mm]	Failure load [N]	
F	80	44	157	17.9	-3.3	osteoporotic	A1	T6-T8	I	M	7072	3232
							A2	T9-T11	L	M	7535	2573
							A3	T12-L2	L	M	2206	2339
							A4	L3-L5	I	M	4078 [*]	3929 [*]
M	92	87	187	24.9	-0.7	normal	B1	T6-T8	L	M	4799	3307
							B2	T9-T11	I	L	4552	2702
							B3	T12-L2	I	M	4176	3294
							B4	L3-L5	L	M	2359	2474
M	80	55	163	20.7	-3.1	osteoporotic	C1	T6-T8	I	M [*]	3251	1780
							C2	T9-T11	L	M	1462	1386
							C3	T12-L2	L	M	1017	1275
							C4	L3-L5	I	M + L	-	-

*The lower vertebra had only slightly collapsed, whereas the middle one showed considerably more damage. Therefore, this specimen was analyzed as if failure occurred in the middle vertebra.

* Whereas the experiments showed failure in the middle vertebra, the FE models predicted the lower vertebra to fail. Therefore, specimen A4 was excluded from stiffness and load to failure analyses.

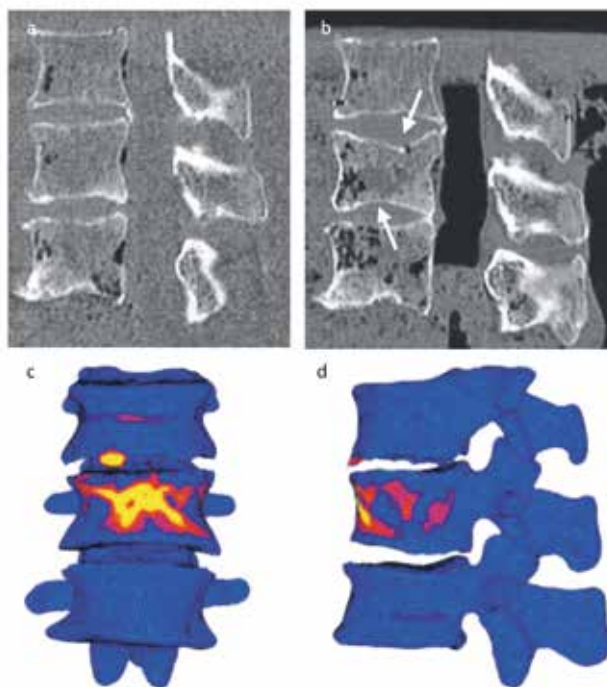


Figure 2 Finite element model predictions of a fracture location, showing areas of plastic deformity (indicated in red/orange/yellow), with experimental CT scans showing failure in the corresponding vertebra. (a) Pre-experimental CT scan; (b) post-experimental CT scan with the arrows indicating endplate failure; (c) plastic deformation located mainly in the middle vertebral body shown in anterior view; (d) plastic deformation located mainly in the middle vertebral body shown in lateral view. Specimen shown: A3.

Stiffness

There was a significant, strong correlation between the experimental and FE predicted stiffness when the material models by Keyak et al. ($R^2 = 0.674$, $p < 0.01$), Kopperdahl et al. ($R^2 = 0.637$, $p < 0.01$), and Morgan et al. ($R^2 = 0.688$, $p < 0.01$) were implemented (Figure 4). Of these, no one was clearly superior. For Ouyang et al.'s material model stiffness could weakly or moderately be predicted, depending on whether or not the strain rate factor was included (without strain rate factor: $R^2 = 0.561$, $p < 0.05$; with strain rate factor: $R^2 = 0.370$, $p > 0.05$) (Figure 4). While the material models by Keyak et al., Kopperdahl et al., and Morgan et al. overpredicted the stiffness in all specimens, it was underestimated in most specimens when Ouyang et al. with strain rate factor was applied (Figure 4).

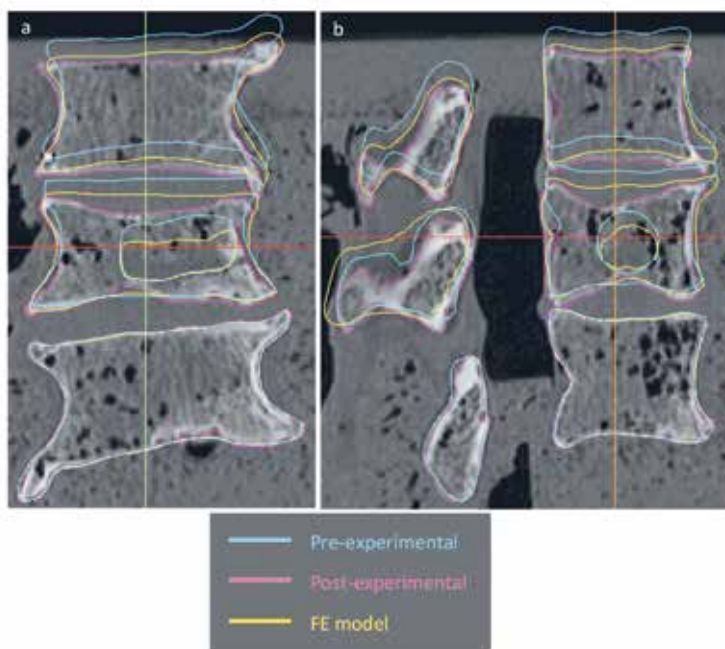


Figure 3 Vertebral contours comparing experimental and FE predicted 3D deformation of the entire specimen in the (a) mid frontal view and (b) mid sagittal view. This representative specimen shows that in most cases deformation of the lower vertebrae was correctly predicted by the FE models, illustrated by overlapping pre- and post-experimental contours as well as FE model contour. In addition, in the experiments often substantial fractures were seen in the endplates, whereas this was not observed in the simulations. Specimen shown: A3.

Load to failure

The load to failure could be weakly predicted: R^2 ranged from 0.219 to 0.247 ($p > 0.05$) (Figure 4). The slopes of the regressions by Keyak et al. (slope = 1.1), Kopperdahl et al. (slope = 0.85) and Morgan et al. (slope = 1.17) were closer to one than the slopes of simulations by Ouyang et al. (without strain rate factor: slope = 0.37) (Figure 4). None of the models of Keyak et al., Kopperdahl et al. or Morgan et al. could be appointed as being superior. When implementing the material model by Ouyang et al. with strain rate factor, the prediction of load to failure was very weak ($R^2 = 0.165$, $p > 0.05$). Furthermore, the FE models based on material models by Keyak et al. and Morgan et al. overestimated the load to failure, while those based on Ouyang et al., irrespective of the strain rate factor, underestimated the load to failure (Figure 4). Implementing Kopperdahl et al.'s material model resulted in some specimens to be overestimated and some to be underestimated.

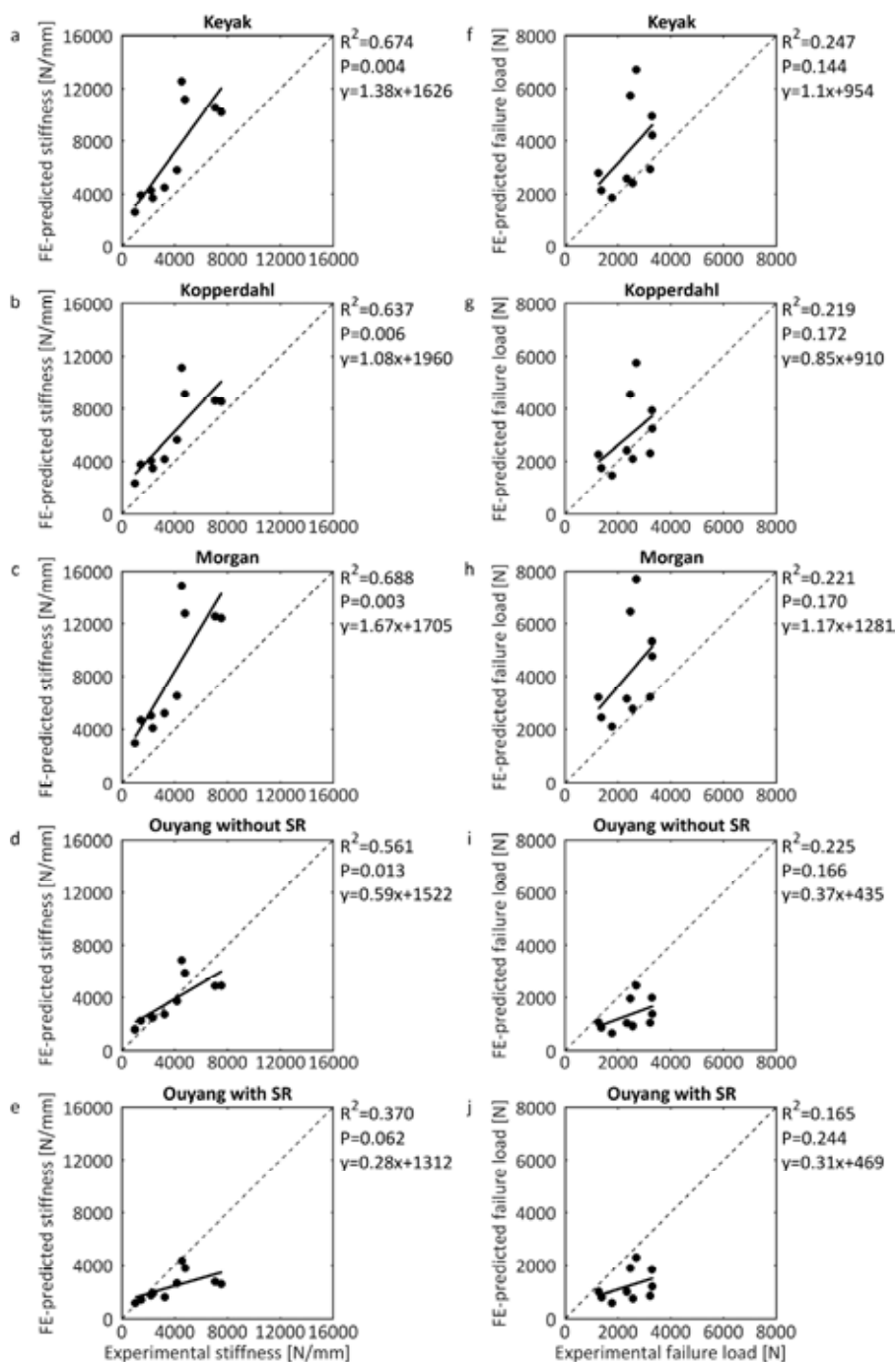


Figure 4 Linear regression of the experimentally measured stiffness *versus* the stiffness predicted by the finite element (FE) model (a-e) and experimentally measured load to failure *versus* the load to failure predicted by the FE model (f-j) for the different implemented material models. SR: strain rate factor.

Discussion

This study aimed to develop a case-specific non-linear FE model of 3-segment spinal units able to predict the failure behavior in terms of (a) the vertebra predicted to fail; (b) the deformation of the vertebrae; (c) stiffness; and (d) load to failure. For this purpose, we also studied the effect of different material models.

To obtain a more realistic biomechanical environment we performed experimental tests and created FE models of 3-segment units instead of isolated vertebrae. Although we are convinced that this approach is more clinically relevant than considering single vertebrae, it also generated additional challenges. When testing three consecutive vertebrae, it is not obvious that the vertebra to fail is correctly predicted by the FE models. Nevertheless, in our study all but one predictions were accurate. When examining the predicted fracture location in more detail, however, it appeared that the predicted specimens' 3D deformation did not completely match with the measured deformation, particularly in cases of endplate failure. We also showed that most FE models did often not converge to a point where the full experimental displacement was reached. Possibly, the predicted and experimentally measured 3D deformation would have corresponded better when the convergence problems are solved. Further improvements of the model in this respect are required.

There have been several attempts to predict compressive stiffness of single vertebrae, with a wide range of predictive capability: $R^2 = 0.50 - 0.81$ [8-10, 33-36]. We reported on structural stiffness of models comprising three vertebrae and two IVDs. Despite the increased complexity of our model, we obtained similar results when the bone material models by Keyak et al., Kopperdahl et al. or Morgan et al. were implemented.

In contrast, the current study could not predict vertebral load to failure as accurately as previous studies. While previous QCT based FE studies on single vertebra reported strong to very strong correlations ($R^2 = 0.76 - 0.96$ [6-10, 33, 36-38]), the correlations we obtained were weak, irrespective of the material model obtained. However, comparisons are complicated due to the wide spread in the criteria used to indicate (or quantify) failure, and in some cases these criteria were fitted to match the experimental data. In the current study, we simulated post-yield plasticity, thereby modeling the full failure process, rather than fitting an 'arbitrary' FE strength criterion to the experimental strength values. Our attempt to more realistically simulate vertebral failure seems, for now, not yet sufficient for obtaining an accurate prediction. However, we do believe that by simulating the actual failure process we will eventually obtain a more robust and true prediction of vertebral failure than in cases where failure criteria are used which may not be applicable under varying clinical circumstances.

The poorer strength prediction may be due to several differences between previous studies and the current models, in terms of modelling approach, medical imaging data that was used for the models, and the loading configuration. Firstly, previous models

have been based on single vertebrae, thereby neglecting the posterior elements including the facet joints, while these are known to carry up to 33% of the axial load [39]. Conversely, the current study included three consecutive vertebrae with the intervertebral discs (IVDs). Loading via IVDs has shown to increase the strain levels in vertebral body, especially in the endplate [40]. Lu et al. [41] and Maquer et al. [42] investigated whether strength predictions computed from high resolution (HR)-pQCT based FE models of human vertebral bodies were influenced by the choice of boundary condition (PMMA vs. IVD). Both studies suggested that adding the IVDs to vertebral body models is not very contributive until fully validated patient-specific IVD models become available. In the current study a simplified disc was implemented, with similar properties as the IVDs modeled by Maquer et al. and Lu et al. Possibly, the mechanical representation of the IVD in our model is too simplistic, resulting in nonrealistic deformation, particularly in the endplate. This might also explain why the FE models did not show endplate collapse, whereas we did find that in the experiments.

The inaccurate prediction of endplate failure may also be due to the fact that CT scans were used with clinical settings instead of high-resolution CT scans. Similar resolution scans [6, 9] have previously been used to successfully predict vertebral strength in single vertebra models ($R^2 = 0.8 - 0.86$). However, the endplate and cortex of the vertebra are quite thin, with a thickness of approximately 0.1 - 1.25 mm [43-45]. Due to partial volume effects, the endplates and cortical shell may not have been captured properly in the FE model. An alternative approach, as is adopted by others [7, 8, 37, 46], could be to add an extra shell to the vertebral body, representing the cortex and/or endplates. Chevalier et al. [34] demonstrated that adding an explicit cortex stiffened and strengthened their HR-QCT models. Since most of our models already overestimated stiffness and strength, adding a shell would most probably not improve our results, particularly since our models already had difficulties capturing endplate fractures.

Furthermore, we performed only compression testing, while the loading conditions of daily living also include flexion and other loading modes. From a practical point of view, a compression test is easier to execute than tests that include bending, especially when using 3-segment spinal units. In our experimental setup (and in our models), however, the specimens were allowed to 'pivot' around the load application point, thereby inducing forward or lateral bending motions. Although the performance of FE models comprising single vertebrae is well known for uniform compression, the ability to predict vertebral strength under non-uniform loading conditions is less clear. The predictive capacity in axial compression might not be indicative of its capacity in bending, as it was previously shown that it is difficult to predict the strength of isolated vertebral bodies in anterior bending ($R^2 = 0.34 - 0.40$) [47]. However, other FE models were able to accurately predict vertebral strength when anterior wedge shape fractures were experimentally induced in single vertebral bodies ($R^2 = 0.77 - 0.79$) [11, 36]. Given these inconsistencies in literature, further research into the effect of loading configuration is required.

Moreover, we showed that the correlation between predicted and experimental fracture loads did not strongly depend on the material model, but the stiffness predictions did. For both stiffness and load to failure, FE models based on the material models by Keyak et al. [14] and Morgan et al. [16, 17] resulted in overpredictions of the experimental measurements, whereas models based on Ouyang et al.'s equations [18] led to underpredictions. Similarly, Silva et al. [48] predicted fracture load and stiffness in midsagittal sections of human vertebral bodies by implementing modulus and strength from density, based on Keller [19] and Kopperdahl and Keaveny (in the paper referred to as 'personal communication, 1995'). They also found that the predicted fracture loads did not strongly depend on the material density-elastic property relations, whereas the stiffness values were highly affected by the material of choice. Stiffness was typically underestimated by a factor of 2-3 on the basis of the Keller relations and was overestimated by a factor of 2-3 on the basis of the Kopperdahl and Keaveny relations.

This work shows that, in its current state, our FE models may be used to identify the weakest vertebra, but that substantial improvements are required in order to quantify *in vivo* failure loads.

Firstly, the FE model might profit from more realistic IVD models [41, 42]. In contrast to the bone material behavior, the IVD properties used in this study were not case-specific but obtained from literature. However, both the type of material model and values for coefficients used in previous FE studies highly varied [25, 27, 28]. The effect of these varying parameters on predictions of vertebral stiffness and/or bone strength is not well investigated. Therefore, effort could be put in determining (case-specific) mechanical properties of IVD tissue and, subsequently, in investigating how implementing these properties in FE models affects the failure behavior of both single vertebra and 3-segment spinal units. In addition, gaining more insight into the effect of IVD properties on endplate failure would be valuable, as endplate failure could not be captured correctly by the current FE model. For this reason, emphasis should also be put on further characterizing and adequately simulating the endplates' mechanical properties.

In addition, in case of sufficient resources and anatomical specimens, it would be interesting to combine testing of 3-segment spinal units with single vertebra tests. In this way, the validity of the material models can be better tested.

Lastly, whereas in the experiments soft tissues, including the spinal ligaments and facet capsules, were left intact, these structures were not accounted for in the FE simulations. Spinal ligaments may contribute to the specimens' stiffness and strength, especially when moving in flexion, extension or lateral bending. As we allowed the specimens to pivot around the load application point, such movements could occur. Adding ligaments and facet capsules to the FE model provides loading conditions being more realistic and better mimicking the experimental conditions, which potentially results in a better predictive capacity of the FE model.

Conclusion

In conclusion, whereas the FE model was able to correctly indicate which vertebrae failed during the experiments, it had difficulties predicting the 3D deformation of the specimens, particularly in cases of endplate failure. In addition, stiffness could be strongly predicted by our model, but we obtained weak correlations between FE predicted and experimentally determined vertebral strength. Therefore, this work showed that, in its current state, our FE models may be used to identify the weakest vertebra, but that substantial improvements are required in order to quantify *in vivo* failure loads.

Acknowledgments

We would like to thank Richard van Swam for his technical assistance and practical help with the experiments, the Department of Anatomy for providing the cadavers, and Willeke van Boekel-Geurts, Peter van Kollenburg for their assistance with CT scanning, Marga Ouwens and Merijn Janssen for making the DEXA scans, and Jasper Homminga and Yan Jiang for their help with finite element modeling.

References

1. Coleman RE. Skeletal complications of malignancy. *Cancer* 1997;80(8 Suppl):1588-1594.
2. Gralow J, Tripathy D. Managing metastatic bone pain: the role of bisphosphonates. *J Pain Symptom Manage* 2007;33(4):462-472.
3. Costa L, Badia X, Chow E, Lipton A, Wardley A. Impact of skeletal complications on patients' quality of life, mobility, and functional independence. *Support Care Cancer* 2008;16(8):879-889.
4. Coleman RE. Metastatic bone disease: clinical features, pathophysiology and treatment strategies. *Cancer Treat Rev* 2001;27(3):165-176.
5. Carpenter RD. Finite element analysis of the hip and spine based on quantitative computed tomography. *Curr Osteoporos Rep* 2013;11(2):156-162.
6. Crawford RP, Cann CE, Keaveny TM. Finite element models predict in vitro vertebral body compressive strength better than quantitative computed tomography. *Bone* 2003;33(4):744-750.
7. Imai K, Ohnishi I, Bessho M, Nakamura K. Nonlinear finite element model predicts vertebral bone strength and fracture site. *Spine (Phila Pa 1976)* 2006;31(16):1789-1794.
8. Liebschner MA, Kopperdahl DL, Rosenberg WS, Keaveny TM. Finite element modeling of the human thoracolumbar spine. *Spine (Phila Pa 1976)* 2003;28(6):559-565.
9. Buckley JM, Loo K, Motherway J. Comparison of quantitative computed tomography-based measures in predicting vertebral compressive strength. *Bone* 2007;40(3):767-774.
10. Chevalier Y, Charlebois M, Pahr D, Varga P, Heini P, Schneider E, Zysset P. A patient-specific finite element methodology to predict damage accumulation in vertebral bodies under axial compression, sagittal flexion and combined loads. *Comput Methods Biomech Biomed Engin* 2008;11(5):477-487.
11. Dall'Ara E, Pahr D, Varga P, Kainberger F, Zysset P. QCT-based finite element models predict human vertebral strength in vitro significantly better than simulated DEXA. *Osteoporos Int* 2012;23(2):563-572.
12. Derix LC, van Aken JB, Janssen D, Snyers A, van der Linden YM, Verdonchot N, Tanck E. The assessment of the risk of fracture in femora with metastatic lesions: comparing case-specific finite element analyses with predictions by clinical experts. *J Bone Joint Surg Br* 2012;94(8):1135-1142.
13. Tanck E, van Aken JB, van der Linden YM, Schreuder HW, Binkowski M, Huizenga H, Verdonchot N. Pathological fracture prediction in patients with metastatic lesions can be improved with quantitative computed tomography based computer models. *Bone* 2009;45(4):777-783.
14. Keyak JH, Kaneko TS, Tehranzadeh J, Skinner HB. Predicting proximal femoral strength using structural engineering models. *Clin Orthop Relat Res* 2005(437):219-228.
15. Kopperdahl DL, Morgan EF, Keaveny TM. Quantitative computed tomography estimates of the mechanical properties of human vertebral trabecular bone. *J Orthop Res* 2002;20(4):801-805.
16. Morgan EF, Bayraktar HH, Keaveny TM. Trabecular bone modulus-density relationships depend on anatomic site. *J Biomech* 2003;36(7):897-904.
17. Morgan EF, Keaveny TM. Dependence of yield strain of human trabecular bone on anatomic site. *J Biomech* 2001;34(5):569-577.
18. Ouyang J, Yang GT, Wu WZ, Zhu QA, Zhong SZ. Biomechanical characteristics of human trabecular bone. *Clin Biomech (Bristol, Avon)* 1997;12(7-8):522-524.
19. Keller TS. Predicting the compressive mechanical behavior of bone. *J Biomech* 1994;27(9):1159-1168.
20. Keaveny TM, Pinilla TP, Crawford RP, Kopperdahl DL, Lou A. Systematic and random errors in compression testing of trabecular bone. *J Orthop Res* 1997;15(1):101-110.
21. Kopperdahl DL, Keaveny TM. Yield strain behavior of trabecular bone. *J Biomech* 1998;31(7):601-608.
22. Groenen KHJ, Janssen D, Van der Linden YM, Kooloos J, Homminga J, Verdonchot N, Tanck E. Inducing targeted failure in cadaveric testing of 3-segment spinal units with and without simulated metastases. *Med Eng Phys*;In press.
23. Whyne CM, Hu SS, Lotz JC. Burst fracture in the metastatically involved spine: development, validation, and parametric analysis of a three-dimensional poroelastic finite-element model. *Spine (Phila Pa 1976)* 2003;28(7):652-660.

24. Whyne CM, Hu SS, Workman KL, Lotz JC. Biphasic material properties of lytic bone metastases. *Ann Biomed Eng* 2000;28(9):1154-1158.
25. Dreischarf M, Zander T, Shirazi-Adl A, Puttlitz CM, Adam CJ, Chen CS, Goel VK, Kiapour A, Kim YH, Labus KM, Little JP, Park WM, Wang YH, Wilke HJ, Rohlmann A, Schmidt H. Comparison of eight published static finite element models of the intact lumbar spine: predictive power of models improves when combined together. *J Biomech* 2014;47(8):1757-1766.
26. Shirazi-Adl SA, Shrivastava SC, Ahmed AM. Stress analysis of the lumbar disc-body unit in compression. A three-dimensional nonlinear finite element study. *Spine (Phila Pa 1976)* 1984;9(2):120-134.
27. Schmidt H, Kettler A, Rohlmann A, Claes L, Wilke HJ. The risk of disc prolapses with complex loading in different degrees of disc degeneration - a finite element analysis. *Clin Biomech (Bristol, Avon)* 2007;22(9):988-998.
28. Clouthier AL, Hosseini HS, Maquer G, Zysset PK. Finite element analysis predicts experimental failure patterns in vertebral bodies loaded via intervertebral discs up to large deformation. *Med Eng Phys* 2015;37(6):599-604.
29. Gustafson HM, Crompton PA, Ferguson SJ, Helgason B. Comparison of specimen-specific vertebral body finite element models with experimental digital image correlation measurements. *J Mech Behav Biomed Mater* 2017;65:801-807.
30. Helgason B, Perilli E, Schileo E, Taddei F, Brynjolfsson S, Viceconti M. Mathematical relationships between bone density and mechanical properties: a literature review. *Clin Biomech (Bristol, Avon)* 2008;23(2):135-146.
31. Galante J, Rostoker W, Ray RD. Physical Properties of Trabecular Bone. *Calcif Tissue Res* 1970;5(3):236-&.
32. Keyak JH, Lee IY, Skinner HB. Correlations between orthogonal mechanical properties and density of trabecular bone: use of different densitometric measures. *J Biomed Mater Res* 1994;28(11):1329-1336.
33. Chevalier Y, Pahr D, Charlebois M, Heini P, Schneider E, Zysset P. Cement distribution, volume, and compliance in vertebroplasty: some answers from an anatomy-based nonlinear finite element study. *Spine (Phila Pa 1976)* 2008;33(16):1722-1730.
34. Chevalier Y, Pahr D, Zysset PK. The role of cortical shell and trabecular fabric in finite element analysis of the human vertebral body. *J Biomech Eng* 2009;131(11):111003.
35. Matsuura Y, Giambini H, Ogawa Y, Fang Z, Thoreson AR, Yaszemski MJ, Lu L, An KN. Specimen-specific nonlinear finite element modeling to predict vertebrae fracture loads after vertebroplasty. *Spine (Phila Pa 1976)* 2014;39(22):E1291-1296.
36. Pahr DH, Schwiedrzik J, Dall'Ara E, Zysset PK. Clinical versus pre-clinical FE models for vertebral body strength predictions. *J Mech Behav Biomed Mater* 2014;33:76-83.
37. Imai K. Analysis of vertebral bone strength, fracture pattern, and fracture location: a validation study using a computed tomography-based nonlinear finite element analysis. *Aging Dis* 2015;6(3):180-187.
38. Mirzaei M, Zeinali A, Razmjoo A, Nazemi M. On prediction of the strength levels and failure patterns of human vertebrae using quantitative computed tomography (QCT)-based finite element method. *J Biomech* 2009;42(11):1584-1591.
39. Binder DS, Nampiaparampil DE. The provocative lumbar facet joint. *Curr Rev Musculoskelet Med* 2009;2(1):15-24.
40. Fields AJ, Lee GL, Keaveny TM. Mechanisms of initial endplate failure in the human vertebral body. *J Biomech* 2010;43(16):3126-3131.
41. Lu Y, Maquer G, Museyko O, Puschel K, Engelke K, Zysset P, Morlock M, Huber G. Finite element analyses of human vertebral bodies embedded in polymethylmethacrylate or loaded via the hyperelastic intervertebral disc models provide equivalent predictions of experimental strength. *J Biomech* 2014;47(10):2512-2516.
42. Maquer G, Schwiedrzik J, Zysset PK. Embedding of human vertebral bodies leads to higher ultimate load and altered damage localisation under axial compression. *Comput Methods Biomech Biomed Engin* 2014;17(12):1311-1322.
43. Wang Y, Battie MC, Boyd SK, Videman T. The osseous endplates in lumbar vertebrae: thickness, bone mineral density and their associations with age and disk degeneration. *Bone* 2011;48(4):804-809.

44. Zehra U, Robson-Brown K, Adams MA, Dolan P. Porosity and Thickness of the Vertebral Endplate Depend on Local Mechanical Loading. *Spine (Phila Pa 1976)* 2015;40(15):1173-1180.
45. Silva MJ, Wang C, Keaveny TM, Hayes WC. Direct and computed tomography thickness measurements of the human, lumbar vertebral shell and endplate. *Bone* 1994;15(4):409-414.
46. Imai K, Ohnishi I, Yamamoto S, Nakamura K. In vivo assessment of lumbar vertebral strength in elderly women using computed tomography-based nonlinear finite element model. *Spine (Phila Pa 1976)* 2008;33(1):27-32.
47. Buckley JM, Cheng L, Loo K, Slyfield C, Xu Z. Quantitative computed tomography-based predictions of vertebral strength in anterior bending. *Spine (Phila Pa 1976)* 2007;32(9):1019-1027.
48. Silva MJ, Keaveny TM, Hayes WC. Computed tomography-based finite element analysis predicts failure loads and fracture patterns for vertebral sections. *J Orthop Res* 1998;16(3):300-308.



7

Combining musculoskeletal
and finite element modeling
to predict spinal failure
under physiological load cases.
An exploratory study

Karlijn H.J. Groenen, Riza Bayoglu, Yvette M. van der Linden, Christopher P. Cop,
Pètra M. Braam, Dennis Janssen, Nico Verdonshot, Esther Tanck.

Introduction

When spinal bone metastases in patients with cancer progress, there is a risk of developing pathological fractures with pain and possibly also neurological injury becoming clinically evident. Since such adverse events dramatically affect the quality of life of the patient, they should be prevented as much as possible [1-3]. Preventing skeletal complications requires an accurate assessment of the fracture risk. Due to the absence of validated guidelines or an established predefined set of risk factors, however, it is at the moment unfeasible for clinicians to assess the fracture risk [4].

Quantitative computed tomography (QCT)-based case-specific finite element (FE) models show great promise to improve these fracture risk predictions. Previous work has demonstrated that FE models comprising single vertebrae can provide accurate predictions of vertebral stiffness and strength, when compared to *in vitro* experiments [5-10]. In this thesis we developed an FE model consisting of three consecutive vertebrae with corresponding discs (3-segment spinal unit), thereby providing a more realistic anatomical configuration with load bearing discs and vertebral bodies above and below the vertebral body of interest.

When assessing fracture risk not only bone strength should be considered, but also the loads applied to the bone should be taken into account. Current FE models on failure behavior mostly use fairly simple loading conditions, for example resembling upright standing, mainly to simulate experimental loading conditions in order to validate the models. Such simplified load cases, however, do not resemble the loads imposed on the spine during activities in daily life and might, therefore, be suboptimal for *in vivo* fracture risk prediction. In fact, loading scenarios such as forward flexion, lateral bending, or axial rotation, have demonstrated to affect the risk of fracture initiation in metastatically affected vertebrae [11].

The *in vivo* loads acting on the spinal column are a complex combination of joint contact forces, ligament forces, and muscle forces. Hence, incorporating joint contact forces, ligament forces, and muscle forces into the loading profile results in a more physiological loading condition. These forces can be estimated using musculoskeletal modeling. Musculoskeletal models apply mechanical principles to a system composed of bones, muscles, and ligaments in order to calculate joint contact forces resulting from gravitational force and the forces produced by the muscles and ligaments. As such, the load imposed on the spine during daily activities can be determined. Applying these sophisticated loading regimes to patient-specific FE models could provide more physiological fracture predictions.

In this exploratory study, we applied the workflow for generating FE models of 3-segment spinal units developed in Chapter 6 to a first patient case. We combined musculoskeletal modeling and FE modeling and aimed to demonstrate that modeling physiological load cases instead of a simple loading regime can significantly affect failure predictions by patient-specific FE models in a patient with spinal bone metastases.

Methods

Prospective patient study

The Department of Radiotherapy (Radboud university medical center) conducts a randomized prospective study in which patients with symptomatic spinal bone metastases are randomized between conventional radiotherapy (1 x 8 Gy) or stereotactic radiotherapy (1 x 20 Gy) to relieve pain (palliative treatment) (Principal Investigator: dr. Pètra Braam, RACOST, ClinicalTrials.gov Identifier: NCT02407795) [12]. Ethical approval was obtained by the local medical ethical committee. Patients with a maximum of two consecutive or noncontiguous vertebrae involved by tumor, no or mild neurological signs, and a life expectancy of >6 weeks are included in this study. Patients with spinal instability or neurological deficit resulting from bony compression of neural structures, or a pathological or impending fracture needing surgical fixation are not eligible for inclusion. Further in- and exclusion criteria are depicted in Table 1.

Table 1 In- and exclusion criteria.

Inclusion criteria
<ul style="list-style-type: none">- Histologically proven solid tumor with radiological diagnosis of spinal metastases- Pain score minimum 2 on 11-point scale (0 = no pain to 10 = worst imaginable pain)- Maximum of 2 consecutive or noncontiguous vertebrae involved by tumor at current level of interest- No or mild neurological signs (radiculopathy, dermatomal sensory change, and decreased muscle strength of involved extremity)- Karnofsky performance status ≥ 60- World Health Organization performance status ≥ 2- Life expectancy >6 weeks- Age ≥ 18 years- Non-pregnant, non-lactating female patients. Sexually active patients of childbearing potential must implement effective contraceptive practices during study.- Written informed consent
Exclusion criteria
<ul style="list-style-type: none">- History of previous radiotherapy to the spine at the current level of interest or overlapping location- Spinal instability or neurological deficit resulting from bony compression of neural structures- Pathological fracture or impending fracture needing surgical fixation- Prior surgery to the spine at the current level of interest or overlapping location- Clinical signs of spinal cord compression or severe neurological deficits- Patients with a pacemaker such that MRI cannot be performed or the treatment cannot be delivered safely- Patients not able to undergo MRI- Earlier nuclear medicine treatment, for example strontium 89 treatment- Pregnancy- Altered mental status that would prohibit the understanding and giving of informed consent

Before and three months after radiotherapy treatment patients undergo QCT and magnetic resonance imaging (MRI) scanning. In addition, patients fill out questionnaires

on physical activity (IPAQ), quality of life (EORTC QLQ-C15-PAL and EORTC QLQ-BM22), and pain (BPI), but these are not included in the current exploratory study. Through their medical records, the patients are followed until either a fracture occurs, or until death, as competing risk, whichever occurs first. The occurrence of a (radiological) vertebral fracture or collapse is confirmed using CT and/or MRI scans.

Patient case

For this exploratory study, our department collaborates with the RACOST study team to study the predictive power of the FE model. We selected one patient from the patient study (female; 64 years at inclusion, body weight: 69 kg; body height: 179 cm; primary tumor: melanoma). This patient had an osteolytic lesion predominantly in the anterior border of the fourth lumbar (L4) vertebral body (Figure 1). Approximately 50% of the vertebral body was affected by tumor tissue. Pre-treatment, alignment of the spine was normal and there was no collapse of the vertebral body. The posterior elements of the spine were not affected by metastatic tissue. Three months after radiotherapy (1 x 20 Gy), radiological evaluation demonstrated a minor collapse of the L4 endplate (Figure 1). At that time, the patient did not report symptoms indicating this collapse. However, 11 months after treatment, the patient's pain severely increased. Subsequent radiographs revealed a further increased collapse of the L4 endplate (reported as being a pathological fracture) as well as ventral and dorsal retropulsion of bony fragments, presumably also in the spinal canal (Figure 1). At this point, the patient had no sign of neurological compromise.



Figure 1 Medical imaging of the metastatically affected fourth lumbar (L4) vertebra. (a) CT scan pre-treatment showing the lytic lesion (arrow); (b) CT scan three months after radiotherapy treatment showing a minor collapse of the L4 endplate (arrow); (c) X-ray 11 months after treatment showing a pathological fracture as well as ventral and dorsal (arrow) retropulsion of bony fragments.

Obtaining loading conditions using musculoskeletal modeling

We used the Twente Spine Model to predict compression and shear forces at the intervertebral joints during physiological movements [13]. In brief, the Twente Spine Model is a complete and coherent musculoskeletal model (MSM) of the entire human spine and is based on two anatomical datasets obtained from one embalmed cadaver (male; 79 years; height: 154 cm; mass: 51 kg) [14, 15]. In this left-right symmetrical MSM, bones were idealized as rigid body segments and muscle-tendon elements as force actuators (Figure 2). A local reference frame for each vertebra was established. The origin of the local reference frame was located at the centroid of the vertebral body and the reference axes were based on vertebral landmarks [16]. The model uses the inverse dynamics method to predict muscle and joint forces based on an optimization function which minimizes the muscle fatigue.

In total, 351 muscle-tendon elements (per body side) were included for 49 muscles. Intervertebral articulations were modeled as spherical joints with the center of rotation based on literature [17]. In the MSM we modeled the stiffness provided by the discs, ligaments, and the facet joints using linear torsion springs in three directions and applied these to the intervertebral joints.

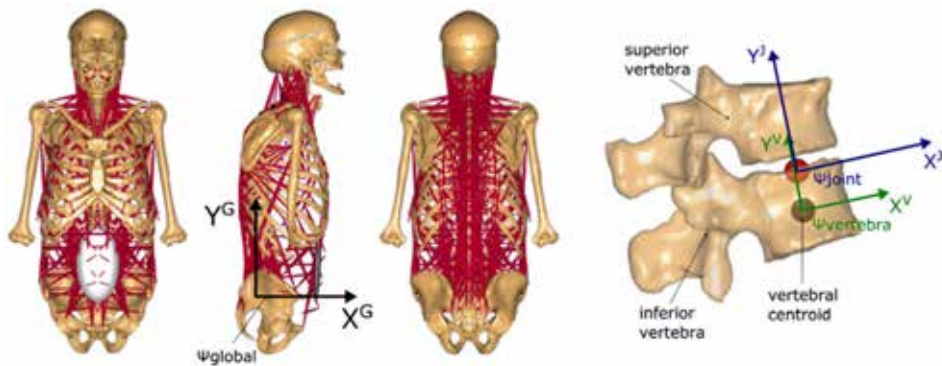


Figure 2 Musculoskeletal model (Twente Spine Model) used in this study, bones are displayed in yellow and muscle-tendon elements in red. The reference frame shown in the sagittal view is the global reference frame (ψ^{global}). Vertebral reference frame (ψ^{vertebra}) and (intervertebral) joint reference frame (ψ^{joint}) are illustrated for one motion segment. The intervertebral compression force is calculated along the y-axis of the joint reference frame.

To enable more realistic comparisons between the MSM and FE model, we scaled the MSM's body height and weight to represent the patient presented in this study. To obtain a scaled MSM, the spinal geometry (bone geometry, joint, and muscle attachment locations) was scaled linearly in three dimensions based on body height ratios. In addition, physiological cross sectional areas (PCSA) of the muscles were scaled based on the strength scaling factor $((\text{subject weight}/\text{model weight})^{2/3})$.

We simulated several quasi-static tasks with the scaled MSM. Each task started from the upright standing position and finished when the prescribed movement was achieved. We only defined the motion between T1 and pelvis segments and partitioned the movement accordingly. In addition, the total trunk motion was distributed between the pelvis and thoracic and lumbar regions of the spine. The following maneuvers were simulated:

1. Flexion (45° and 90°)
2. Extension (15°)
3. Right lateral bending (15°)
4. Left lateral bending (15°)

The resultant joint reaction forces in and the positions of the L2/L3 joint during these maneuvers were calculated with respect to the L5 local reference frame.

FE model generation

An FE model of the patient's L3-L5 spine was generated using the workflow for generating case-specific FE models of 3-segment spinal units described in Chapter 6. The patient's pre-treatment QCT scan was used as input for the FE model. In short, quantitative computed tomography (QCT) images were retrieved (scan settings: 120 kVp; 300 mAs; slice thickness 1.0 mm; pitch 0.938; standard reconstruction; in plane resolution 0.977 mm). Geometric information for the vertebral bone and intervertebral discs (IVDs) was retrieved by segmenting the QCT images (Materialise Mimics 14.0, Materialise NV, Leuven, Belgium). The IVD was discretized into a nucleus pulposus (NP) and annulus fibrosis (AF), with the NP area constituting approximately 40% of the total disc area [18, 19]. The lesion was segmented by an experienced musculoskeletal radiologist. Vertebrae, lesion, and discs were converted into a tetrahedral solid mesh (HyperMesh 2017.1, HyperWorks, Altair Engineering, Inc. Troy, Michigan, United States).

The patient was scanned on top of a calibration phantom, which was positioned at the level of the affected vertebra (Image Analysis, Columbia, Kentucky, United States). Using this phantom, the CT intensities of voxels representing bone tissue were converted into calcium equivalent values. Subsequently, isotropic material properties were assigned to each element based on the work by Keyak et al. [20]. For the upper and lower vertebrae, material behavior was assumed to be linear elastic. In contrast, non-linear elastic-plastic material behavior was assigned to the middle vertebra. More specifically, when the yield stress was reached, plasticity was induced and further defined by an initial ideal plastic phase, subsequent softening, and a final ideal plastic phase. Within the IVD, the NP and AF were modeled using hyperelastic Mooney-Rivlin material models. The AF was further modeled as a composite material with embedded rebar elements used to represent the collagen fiber reinforcement. The fibers were placed circumferentially at $\pm 20^\circ$ with the disc's local transverse plane and only acted in tension. Material properties were obtained from literature (NP: C10 = 0.2; C01 = 0.045;

bulk modulus (κ) = $1.0 \cdot 10^6$ MPa. AF ground substance: C10 = 0.21; C01 = 0.045; κ = $1.2 \cdot 10^6$ MPa. Fibers: Young's modulus (E) = 650 MPa; Poisson's ratio (ν) = 0.33).

FE simulations

Both the experimental and physiological boundary conditions were, consecutively, applied to the model. The workflow for simulating the experimental setup has been described in Chapter 6. The specimen was loaded in axial compression until failure.

To apply the physiological boundary conditions, the global coordinate system of the FE model was transformed to align with the local reference frame of the L5 vertebra in the MSM. This way, L5, being the lower vertebra of the 3-segment spinal unit, could be constrained from translations and rotations in any direction. Subsequently, the FE model was transformed by visually aligning the FE and MSM L5 vertebrae. On the proximal end of the selected 3-segment spinal unit, the L2L3 joint resultant joint reactions forces and positions for all load cases obtained from the MSM were applied to the FE model. The loads and displacements were applied to a node of which the location matched the L2L3 joint location of the MSM. This node was connected to the upper vertebra using rigid body elements type 2 (RBE2). The load cases were applied in a combined force- and displacement-controlled manner and in two consecutive steps. The first step resembled upright standing and in the second step the flexion, extension, and lateral bending maneuvers were simulated.

Step I. Pre-conditioning simulating upright standing:

- A compressive force in the y-direction equal to force in y at $t = 0$ calculated by the MSM was prescribed, representing upright standing.
- Displacements in the x- and z-directions were constrained.

Step II. Load application simulating the maneuvers:

- The forces in the y-direction calculated by the MSM, depending on the maneuvers, were prescribed
- Translation in the forward (+x, flexion), backward (-x, extension), left (-z, left lateral bending), or right (+z, right lateral bending) direction only was prescribed, of which the magnitude corresponded to the magnitude of MSM's L2L3 joint translation.
- Displacements in the irrelevant directions (i.e. z-direction for flexion/extension and x-direction for lateral bending) were constrained.

The FE simulations were performed with MSC Marc (MSC.MARC2013r1; MSC Software Corporation, Santa Ana, California, United States).

Data analysis

In order to compare the structural response of both models, displacements and forces predicted by the MSM were compared to those calculated by the FE model. Subsequently, fracture locations were qualitatively compared between the load cases. In order to compare loads that induced plasticity between axial compression and physiological movements, the load at initial plasticity in axial compression was considered. For this, we calculated the volume percentage of plastic elements (i.e. the summed volume of all elements with plasticity divided over the total volume of L4) at the end of the physiological movements and, subsequently, determined the axial reaction force at the increment in which the same volume percentage elements had turned plastic in the experimental loading configuration.

Results

Comparison between displacements and forces predicted by the MSM and FE model

Table 2 depicts the displacements and forces at the final stage of the applied movements (flexion, extension, lateral bending) predicted by the MSM and FE model. For flexion (45°) and extension, the magnitude of the reaction forces in the x-direction was smaller in the FE model than in the MSM model. Similarly, the displacements predicted in the y-direction were smaller in the FE compared to the MSM model. For the 90° flexion task, the predicted reaction forces in the x-direction were similar for both models, but the displacements were not.

Conversely, for lateral bending, the reaction forces in the z-direction were larger in the FE model than in the MSM model. In addition, the displacements in y-direction predicted by the FE model were larger than the displacements predicted by the MSM.

Comparison between physiological movements and the experimental setup

While in extension and lateral bending no plasticity was observed, a few elements, mainly on the surface of the lesion, became plastic in 45° flexion (Figure 3). In 90° flexion the region of plasticity had slightly increased when compared to the 45° flexion movement (Figure 3).

The load to failure of the specimen in the experimental setup was 3741 N. At this point of failure, plasticity was observed at the posterior part of the vertebral body including its posterior wall (Figure 4).

Table 2 Comparison of the displacements and reaction forces at the L2/L3 joint at the end of the simulations of the MSM and FE model. For all movements, the force in the y-direction and displacements in the x- and z-directions were prescribed. Therefore, the values predicted by the FE are very similar to the values predicted by the MSM (shown in blue). For comparing the responses of the FE and MSM, for flexion and extension the displacement in the y-direction and force in the x-direction should be considered and for lateral bending the displacement in y-direction and force in the z-direction are of most interest (shown in orange). Numbers lower than 0.001 were considered to be 0.

	Flexion 45°		Flexion 90° *		Extension		Left bending		Right bending	
	MSM	FE	MSM	FE	MSM	FE	MSM	FE	MSM	FE
Displacement x [mm]	7.53	7.53	10.69	10.95	-1.73	-1.73	0.02	0	0.02	0
Displacement y [mm]	6.23	2.21	8.31	3.04	-1.74	-1.01	-0.01	-0.23	-0.01	-0.28
Displacement z [mm]	0	0	0	0	0	0	-1.57	-1.57	1.57	1.57
Reaction force x [N] ‡	-721	-515	-689	-679	-471	-84	-524	-144	-522	-146
Reaction force y [N] ‡	756	756	996	1012	326	327	341	341	341	341
Reaction force z [N] ‡	-0.2	12	-0.8	20	-0.3	7	-40	142	40	-129

*This FE simulation did not converge to a point where the full MSM displacement in the x-direction was reached. For comparison with the MSM, the stage of the MSM in which a similar displacement in the x-direction was predicted is depicted.

‡ We corrected for differences in definitions obtained by the MSM and FE model, by flipping the sign of the reaction forces calculated by the FE model.

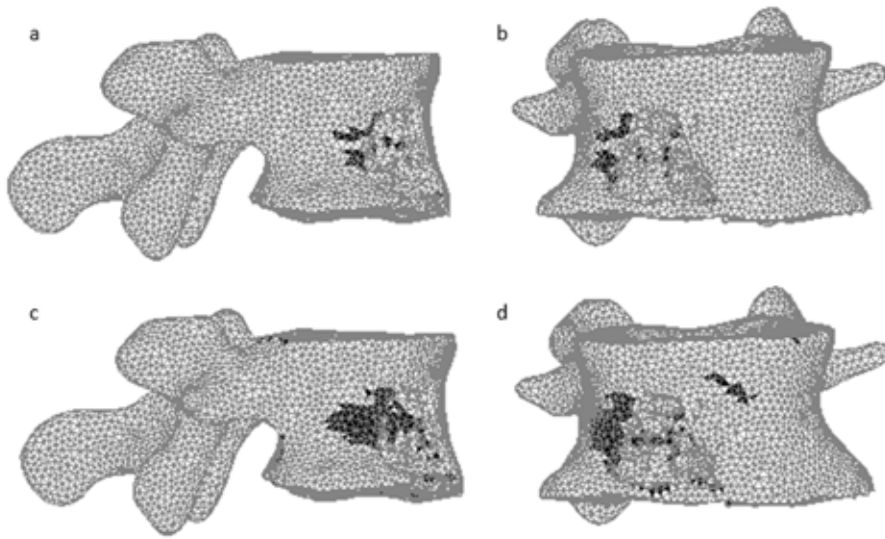


Figure 3 Plasticity (elements shown in black) induced in L4 by 45° flexion (a-b) and 90° flexion (c-d). Sagittal and frontal views are shown.

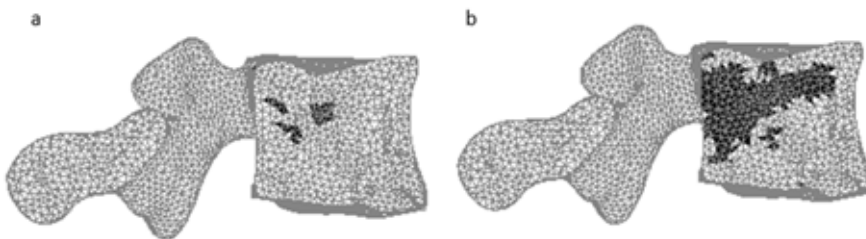


Figure 4 Plasticity (elements shown in black) induced in L4 by an axial compressive load at (a) initial plasticity and (b) structural failure. Cross-sections through the midsagittal plane are shown.

Of the physiological movements, only in flexion plasticity was observed. To compare the spinal loads under flexion and axial compression, we calculated the volume percentage of plastic elements at 45° flexion and, subsequently, determined the axial reaction force at the increment in which the same volume percentage elements had turned plastic in the experimental loading configuration (hereinafter referred to as *axial compression at initial plasticity*) (Figure 4). The load at initial plasticity in axial compression was 2267 N.

Figure 5 illustrates the total joint reaction forces in the end stages of the different physiological loading conditions, as well as the axial reaction forces at initial plasticity and structural failure in the experimental loading configuration. The total joint reaction force at 45° flexion (915 N), in which some plasticity was observed, was considerably

lower than the force required to induce a similar volume percentage of plastic elements in axial compression (2267 N). Furthermore, the force needed to induce failure in axial compression (3741 N) appeared to be approximately 9 times higher than the total joint reaction forces induced by extension (338 N) and lateral bending (left: 396 N; right: 393 N).

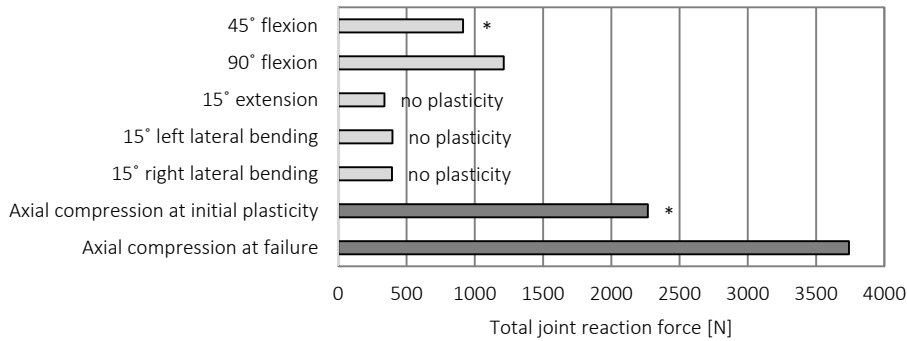


Figure 5 Total joint reaction forces calculated by the FE model for the end stages of the different physiological loading conditions (light grey bars) as well as the axial reaction forces in the experimental loading configuration (dark grey bars). For the experimental loading configuration, the axial reaction force at the increment at which the volume percentage of plastic elements was the same as the volume percentage of plastic elements in 45° flexion (axial compression at initial plasticity) and the axial reaction force at structural failure are depicted. It is shown that the total joint reaction force in flexion was more than two times lower than the force needed to induce the same amount of plasticity under axial compression (bars indicated with *).

Discussion

In this exploratory study physiological load cases predicted using musculoskeletal modeling were applied to an FE model of a real patient with spinal bone metastases who was treated within the prospective RACOST study, and were compared with a load case resembling an *in vitro* experimental setup. The goal of this study was to demonstrate that modeling physiological load cases can have a significant effect on failure predictions when compared to the simulation of a simple loading regime.

Of the physiological load cases, only flexion caused plasticity, although this did not directly lead to structural failure of the vertebral body. Although only a minor amount of plasticity was seen at 45° of flexion, the total joint reaction force in flexion was more than two times lower than the force needed to induce the same amount of plasticity under axial compression. This may indicate that the vertebra under study was more prone to failure under flexion than compression. Also, the location in which plasticity occurred differed between the two loading configurations. Whereas in axial compression plasticity was mostly seen in the posterior part of the vertebral body, in flexion plasticity was mainly observed around the lesion located in the anterior part of the vertebral

body. This emphasizes the importance of testing multiple physiological loading configurations when predicting the *in vivo* fracture risk.

The patient described in the current study sustained a pathological fracture of L4 during follow-up 11 months after stereotactic radiotherapy (1 x 20 Gy). When loading the L3-L5 specimen in axial compression, however, failure was not predicted to occur in L4, but in L3 (data not shown). For this reason, we assigned elastic rather than elastic-plastic material behavior to L3 and L5. It is unknown what movement or activity caused the major collapse in the patient's L4, which may have been different from axial compression. This, therefore, again implies that different loading configurations should be considered when predicting the *in vivo* fracture risk.

For flexion and extension the magnitude of the reaction forces were smaller in the FE model than in the MSM, whereas for lateral bending the reaction forces were larger in the FE model. When underestimating the forces while plasticity being absent, one should be careful with concluding that plasticity is not induced by that specific movement. The absence of plasticity could be caused by the underestimation of the applied forces. Conversely, when the FE model overestimated the forces predicted by the MSM while plasticity being absent, it could be safely concluded that that particular movement did not induce plasticity. Thus, it is highly unlikely that 15° lateral bending would introduce plasticity in this patient.

This study has a considerable number of limitations and should be considered as an exploratory study to assess *in vivo* fracture risk. Firstly, we used a combined force-controlled and displacement-controlled simulation. Ideally, a purely force-controlled simulation should have been used, thereby prescribing only forces in the x-, y- and z-direction. However, adopting this approach led to either numerical convergence problems or non-physiological failure patterns, movements, or reaction forces. An alternative approach would be to prescribe displacements in all directions. However, when performing purely displacement controlled simulations, similar problems were observed. These problems were likely due to a mismatch in dimensions of the MSM and FE model. The MSM was linearly scaled to the FE model based on body height, while differences in spinal curvature and vertebral morphology were ignored, resulting in geometrical differences between the MSM and FE model. Consequently, applying the displacements of the MSM L2L3 joint to the FE model resulted in non-physiological deformations of the spine. Eventually, the resulting joint reaction forces and positions were directly applied to the FE model, which, due to the mismatch in spinal curvature, vertebral morphology, and joint location, may have induced differences in the applied overall joint loads.

Furthermore, the MSM explicitly modeled joint stiffness by using torsional springs, representing the stiffness of the discs, ligaments and facet joints. In contrast, the FE model only included the intervertebral discs and did not take into account stiffness due to spinal ligaments. A discrepancy in joint stiffness between the MSM and FE model may have contributed to the convergence problems. Moreover, we observed that the forces

and displacements predicted by the MSM did not fully match the forces and displacements calculated by the FE model. This may also be due to the discrepancy in spinal dimensions and joint stiffness.

The movements simulated in the current study are not very demanding for the spine. Tasks like lifting an object, forward bending while carrying a weight, or walking downstairs will most likely cause higher loads in the spine. However, the MSM does not have the ability to simulating such movements yet. Hence, future MSM studies on vertebral loads should take these more demanding task in account to enable a more robust probing of vertebral strength.

Conclusion

In conclusion, this study demonstrated a first attempt to combine musculoskeletal and FE modeling in spinal bone metastases in a real patient case. Modeling physiological load cases instead of a simple loading regime significantly affected the failure predictions, indicating that for *in vivo* fracture prediction physiological load cases should be considered. Substantial improvements regarding the FE model, MSM, as well as combining MSMs and FE models are required in order to be able to predict plasticity under physiological loads.

Acknowledgments

We would like to thank Gill McColl for her help with the data management of the RACOST study, and Jasper Homminga and Bart Koopman for their help with developing the musculoskeletal model.

References

1. Bakar D, Tanenbaum JE, Phan K, Alentado VJ, Steinmetz MP, Benzel EC, Mroz TE. Decompression surgery for spinal metastases: a systematic review. *Neurosurg Focus* 2016;41(2):E2.
2. Harel R, Angelov L. Spine metastases: current treatments and future directions. *Eur J Cancer* 2010;46(15):2696-2707.
3. Sutcliffe P, Connock M, Shyangdan D, Court R, Kandala NB, Clarke A. A systematic review of evidence on malignant spinal metastases: natural history and technologies for identifying patients at high risk of vertebral fracture and spinal cord compression. *Health Technol Assess* 2013;17(42):1-274.
4. Fisher CG, DiPaola CP, Ryken TC, Bilsky MH, Shaffrey CI, Berven SH, Harrop JS, Fehlings MG, Boriani S, Chou D, Schmidt MH, Polly DW, Biagini R, Burch S, Dekutoski MB, Ganju A, Gerszten PC, Gokaslan ZL, Groff MW, Liebsch NJ, Mendel E, Okuno SH, Patel S, Rhines LD, Rose PS, Sciubba DM, Sundaresan N, Tomita K, Varga PP, Vialle LR, Vrionis FD, Yamada Y, Fourney DR. A novel classification system for spinal instability in neoplastic disease: an evidence-based approach and expert consensus from the Spine Oncology Study Group. *Spine (Phila Pa 1976)* 2010;35(22):E1221-1229.
5. Crawford RP, Cann CE, Keaveny TM. Finite element models predict in vitro vertebral body compressive strength better than quantitative computed tomography. *Bone* 2003;33(4):744-750.
6. Imai K, Ohnishi I, Bessho M, Nakamura K. Nonlinear finite element model predicts vertebral bone strength and fracture site. *Spine (Phila Pa 1976)* 2006;31(16):1789-1794.
7. Liebschner MA, Kopperdahl DL, Rosenberg WS, Keaveny TM. Finite element modeling of the human thoracolumbar spine. *Spine (Phila Pa 1976)* 2003;28(6):559-565.
8. Buckley JM, Loo K, Motherway J. Comparison of quantitative computed tomography-based measures in predicting vertebral compressive strength. *Bone* 2007;40(3):767-774.
9. Chevalier Y, Charlebois M, Pahr D, Varga P, Heini P, Schneider E, Zysset P. A patient-specific finite element methodology to predict damage accumulation in vertebral bodies under axial compression, sagittal flexion and combined loads. *Comput Methods Biomech Biomed Engin* 2008;11(5):477-487.
10. Dall'Ara E, Pahr D, Varga P, Kainberger F, Zysset P. QCT-based finite element models predict human vertebral strength in vitro significantly better than simulated DEXA. *Osteoporos Int* 2012;23(2):563-572.
11. Tschirhart CE, Finkelstein JA, Whyne CM. Metastatic burst fracture risk assessment based on complex loading of the thoracic spine. *Ann Biomed Eng* 2006;34(3):494-505.
12. Braam P, Lambin P, Bussink J. Stereotactic versus conventional radiotherapy for pain reduction and quality of life in spinal metastases: study protocol for a randomized controlled trial. *Trials* 2016;17:61.
13. Bayoglu R, Galibarov PE, Verdonchot N, Koopman B, Homminga J. Twente spine model: A complete, coherent, and scalable musculoskeletal model of the human spine for investigating spinal loading. *J Biomech Under review*.
14. Bayoglu R, Geeraedts L, Groenen KH, Verdonchot N, Koopman B, Homminga J. Twente spine model: A complete and coherent dataset for musculo-skeletal modeling of the lumbar region of the human spine. *J Biomech* 2017;53:111-119.
15. Bayoglu R, Geeraedts L, Groenen KH, Verdonchot N, Koopman B, Homminga J. Twente spine model: A complete and coherent dataset for musculo-skeletal modeling of the thoracic and cervical regions of the human spine. *J Biomech* 2017;58:52-63.
16. Stokes IA. Three-dimensional terminology of spinal deformity. A report presented to the Scoliosis Research Society by the Scoliosis Research Society Working Group on 3-D terminology of spinal deformity. *Spine (Phila Pa 1976)* 1994;19(2):236-248.
17. Pearcy MJ, Bogduk N. Instantaneous axes of rotation of the lumbar intervertebral joints. *Spine (Phila Pa 1976)* 1988;13(9):1033-1041.
18. Dreischarf M, Zander T, Shirazi-Adl A, Puttlitz CM, Adam CJ, Chen CS, Goel VK, Kiapour A, Kim YH, Labus KM, Little JP, Park WM, Wang YH, Wilke HJ, Rohlmann A, Schmidt H. Comparison of eight published static finite element models of the intact lumbar spine: predictive power of models improves when combined together. *J Biomech* 2014;47(8):1757-1766.

19. Shirazi-Adl SA, Shrivastava SC, Ahmed AM. Stress analysis of the lumbar disc-body unit in compression. A three-dimensional nonlinear finite element study. *Spine (Phila Pa 1976)* 1984;9(2):120-134.
20. Keyak JH, Kaneko TS, Tehranzadeh J, Skinner HB. Predicting proximal femoral strength using structural engineering models. *Clin Orthop Relat Res* 2005(437):219-228.



8

The effect of radiotherapy, and radiotherapy combined with bisphosphonates or RANK ligand inhibitors on bone quality in bone metastases. A systematic review

Karlijn H.J. Groenen, Martin H. Pouw, Gerjon Hannink, Allard J.F. Hosman,
Yvette M. van der Linden, Nico Verdonchot, Esther Tanck.

Radiotherapy and Oncology 2016;119(2):194-201

Introduction

Metastatic bone disease is a common and severe complication in patients with advanced cancer. It develops in up to ~75% of patients with advanced solid cancer [1]. Bone metastases are most often observed in patients with breast (65 - 75%) and prostate (65 - 75%) cancer, but also occur in other metastatic solid cancers [2]. Without treatment, patients with bone metastases may suffer from pain and other debilitating skeletal complications such as pathological fractures or, when vertebrae are affected, neurological complaints such as spinal cord compression [2, 3]; all dramatically affecting the patients' quality of life [1, 4]. In metastatic bone disease, the main goals of treatment are relief of pain and skeletal stabilization with preservation or restoration of (neurological) function, mobility, and quality of life [5].

According to current clinical guidelines, patients confronted with already fractured bones or having large impending lesions in weight bearing bones should be treated with surgical osteosynthesis for immediate stabilization [6-9]. From the perspective of the patient, however, it would be beneficial if metastatic lesions could be sufficiently stabilized using non-invasive treatments, such as local radiotherapy. Radiotherapy can be given either alone, or in combination with systemic therapies (e.g. anticancer treatments with chemotherapy or hormonal therapy, bisphosphonates, and RANK ligand (RANKL) inhibitors) to increase the bone strengthening effect.

Currently, clinicians have difficulties in assessing bony instability based on the available diagnostic imaging data [6, 8, 9] and both radiotherapy and systemic therapies are used widespread to palliate the lesions by reducing pain and, as a secondary effect, to increase the bone mass. As low bone density, such as in patients suffering from osteoporosis and metastatic bone disease, is a strong predictor for future fracture risk, therapeutically increasing bone density might result in a lower fracture risk [10, 11]. Bone fractures are devastating events for patients with bone metastases, as bone fractures are accompanied by pain, stress and anxiety, need for surgery, decreased quality of life and can lead to complications such as spinal cord compression. Therefore, treatment should aim at preventing fractures. In order to use non-invasive modalities for stabilization purposes, it should be determined whether these treatments are effective. And, if so, it should be established what treatment, or combination of treatments, is most effective in improving the bone quality and bone strength of affected bones.

Although radiotherapy has long been established as an effective local treatment for metastatic bone pain [5, 12-16], its use in stabilizing affected bones is based merely on clinical experience. Scientific data underlining this stabilizing effect are scarce. Radiotherapy is thought to first reduce the bone mineral density (BMD) during a short period of time directly after radiotherapy, but subsequently induce re-calcification of the lesion, a process during which new bone is formed [17]. It is generally believed that, in patients responding to radiotherapy, about three months are necessary for the bone to be sufficiently strengthened [17].

In current practice, bisphosphonates (BPs) are also used to increase the bone mass and strength, to prevent future pathological fractures [18-21]. Furthermore, RANKL inhibitors inhibit osteoclast mediated bone resorption [22] and might, therefore, also play a role in increasing bone mass.

The general idea is that the newly formed bone induced by radiotherapy, bisphosphonates, and RANKL inhibitors strengthens the affected bone [23]. The effect of combining radiotherapy and BPs or RANKL inhibitors on bone quality is unknown. As these treatments have different mechanisms of action [24-26], they might have an additive or synergistic effect on the process of re-calcification of metastatically affected bones [27]. Consequently, these treatment combinations might prevent pathological fractures and accompanying neurological problems, depending on the anatomical localization of the lesion, more effectively.

A thorough analysis of the potentially stabilizing effect of non-invasive treatments for patients with metastatically affected bones can aid in the clinical treatment decision making process. Therefore, the aims of this systematic review are to assess the effects of (1) radiotherapy, (2) radiotherapy combined with bisphosphonates, and (3) radiotherapy combined with RANKL inhibitors, on bone quality and bone strength parameters in bone metastases originating from solid tumors.

Methods

Search strategy

PubMed, EMBASE and the Cochrane Library were searched (last search performed November 26th, 2015). No limits were used for PubMed and the Cochrane Library. The search in EMBASE was limited to articles, errata, and reviews. The search strategy included search terms and their synonyms for bone metastases, radiotherapy, bisphosphonates, RANKL inhibitors, bone mineral density, bone quality and bone strength. The search strategy was developed in collaboration with information specialists from the medical library of the Radboud university medical center Nijmegen, the Netherlands. The detailed search strategy is provided in Appendix A. In addition, reference lists of the included studies as well as relevant retrieved narrative and systematic reviews were screened for potentially missed papers.

Study selection

Original studies using radiotherapy, BPs and RANKL inhibitors of any type and dosage were allowed. Both human and animal studies were included. In addition, we allowed all types of study design.

In the screening stage, studies were evaluated based on title and abstract. Studies were excluded if they fulfilled one of the following criteria: (1) No primary study; (2) No bone metastases; (3) No or not only bone metastases originating from solid primary tumors; (4) None of the following as intervention(s): radiotherapy, radiotherapy vs. radiotherapy, radiotherapy vs. radiotherapy + BPs, radiotherapy + BPs, radiotherapy vs. radiotherapy + RANKL inhibitor, or radiotherapy + RANKL inhibitor. As we were not only interested in the 'end effect' (bone strength or fracture) but also in the changes in bone density, we decided that it would be better to have similar mechanisms of metastasizing or tumor growth. Therefore, we solely included studies on metastases originating from solid primary tumors. If eligibility for inclusion could not be decided based on abstract screening, the full text article was retrieved.

Subsequently, full text articles of the selected studies were evaluated for eligibility. Studies were excluded if they met any of criteria 1-4, or one of the following: (5) Article not in English, German, or Dutch; (6) Radiotherapy was not applied locally or directly to bone metastases; (7) None of the following outcome measures, or surrogate outcome measures, were reported: re-calcification, bone density, bone micro-architecture, bone strength, pathological fractures; (8) Outcome measures were not determined at the irradiated side. In addition, papers were excluded if the paper contained data also published in another included paper. In case of a sub study being part of the larger, original study, the original study was included. In case of reported preliminary data the most extended paper was included. Two reviewers (KG, MP) independently screened titles and abstracts and selected full texts for eligibility. Disagreements were resolved by discussion and consensus and if necessary a third reviewer was consulted (YvdL).

Data extraction

KG extracted the data onto a preset data extraction form. This form was pilot tested using 15 articles to check if all variables of interest were successfully extracted. After completing the data extraction, MP reviewed the data extraction form for completeness and accuracy. Next to bibliographic details, we collected data on study design (type of study, key exclusion criteria, number of patients/animals and lesions included, and time of assessment), patient characteristics (primary tumor site, treated site(s)), treatment, and methods used to measure the outcome measures of interest. Outcome measures related to bone quality and bone strength were divided into five principal outcome categories: (1) Radiologic response (any qualitative description of re-calcification), (2) bone density (any quantitative description of bone density), (3) micro-architecture, (4) bone strength, and (5) pathological fractures. Studies had to report on at least one of the defined outcome measure categories. When pathological fractures were reported, time to fracture was also extracted. Other time related parameters, such as follow-up time or survival time, were also extracted when studies reported on fracture rate. If data were only presented graphically, data were manually extracted from these graphs.

Quality assessment

The Quality Assessment Tool for Quantitative Studies developed by the Effective Public Health Practice Project was used to assess methodological quality [28]. Each study was rated as ‘strong’, ‘moderate’, or ‘weak’ on six individual components (selection bias, study design, confounders, blinding, data collection methods, withdrawal and dropouts). An overall global rating was then assigned to each study with studies classified as ‘strong’ (no weak ratings), ‘moderate’ (one weak rating), or ‘weak’ (two or more weak ratings). Two authors (KG and MP) rated the methodological quality of all studies independently. Disagreements were resolved by discussion.

Results

Study selection

The search strategy retrieved 3273 unique records. Subsequent selection procedure resulted in 37 eligible articles. Two additional relevant articles were found via cross-referencing. Thus, 39 studies [17, 29–66] were included in this systematic review (Figure 1). Vassiliou et al. [63, 64] confirmed that both their studies contained unique patient cohorts and, therefore, both studies were included. Although the studies by Foerster et al. [39] and Schlampp et al. [54] had an overlap of about 80% in patient population, they reported on different outcome parameters. Therefore, both studies were included in this systematic review.

Study description and quality assessment

Descriptive data for the included studies are summarized in Appendix B. Of the 39 studies included, three were animal studies and 36 were patient studies. Overall, patient studies varied considerably in terms of study design, type and dose of radiotherapy and BP, type of primary tumor, and location of bone metastases. In addition, different definitions for similar outcome measures were used (Appendix B), similar outcome measures were quantified using different methods (Appendix B), and outcome measures were assessed at different time points after radiotherapy (Appendices C–E). Seven of the 22 patient studies reporting on pathological fractures looked at pathological fractures as primary outcome measure.

Figure 2 gives an overview of study quality assessment. Overall, four, 23 and 12 of the included studies were rated as ‘strong’, ‘moderate’, and ‘weak’, respectively. Seven studies stated that the allocation of the treatment to the treatment groups was randomized. However, only one of these studies mentioned the method of randomization used and provided sufficient details to adequately judge the method. The other six were thus defined as a controlled clinical trial instead of a randomized

controlled clinical trial. Furthermore, 33 of the studies were rated as 'strong' on 'confounders', reflecting the absence of pre-treatment differences between groups. However, 21 out of these 33 studies contained a single intervention group. Therefore, these studies scored 'strong' on 'confounding', as there were no differences between groups. In addition, most prospective studies reported poorly on withdrawals and dropouts. The individual scores of each study are presented in Appendix F.

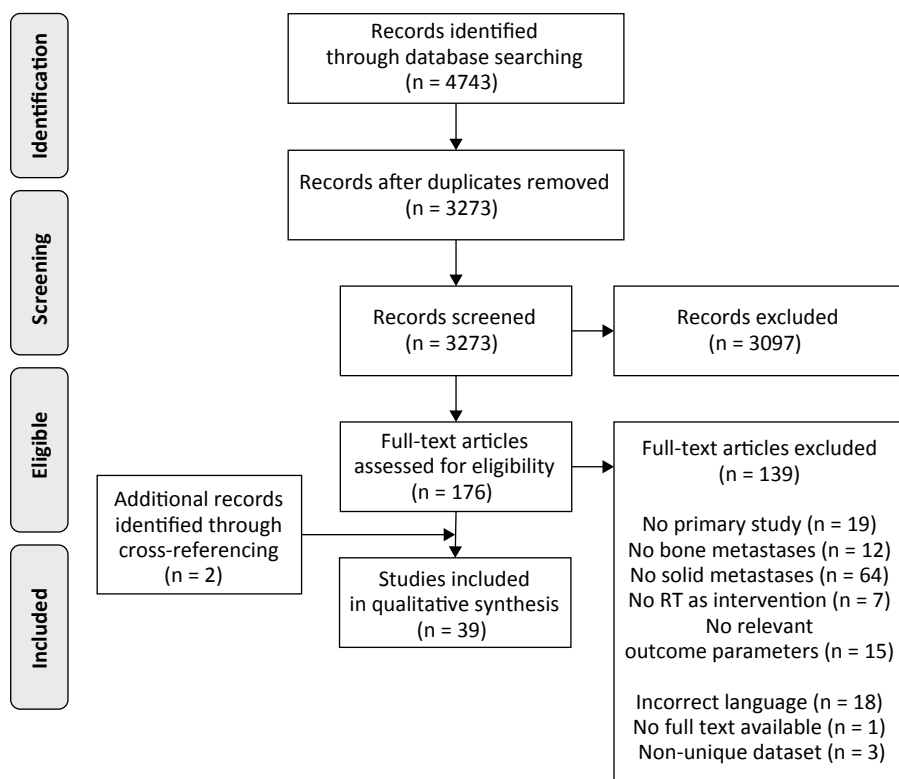


Figure 1 Flow diagram of the systematic review literature and search results.

Animal studies

Three animal studies (Appendix C) investigated differences in bone quality between metastatic bone lesions treated with only radiotherapy and radiotherapy combined with BPs. Arrington et al. [29, 30] used zoledronic acid (ZA) as BP and Krempien et al. [31] used clodronate (CL). Combining ZA with radiotherapy resulted in a significantly higher bone mineral density (BMD), more trabecular bone, and higher strength when compared to radiotherapy alone [29, 30]. Adding ZA to the radiotherapy treatment could even restore bone quality to those of healthy controls [29, 30]. Krempien et al. [31] demonstrated that starting CL 3-6 days before radiotherapy resulted in a BMD and

fractional trabecular volume similar to healthy bone, whereas not using CL or starting CL simultaneously with radiotherapy resulted in a bone quality which was lower than that of healthy bone. Both studies by Arrington et al. [29, 30] showed that treating bone lesions with radiotherapy only resulted in a fractional trabecular volume and bone strength similar to metastatic bone that received no treatment at all.

Correlations between changes in bone mineral density, bone micro-architecture and strength were not reported in the included animal studies.

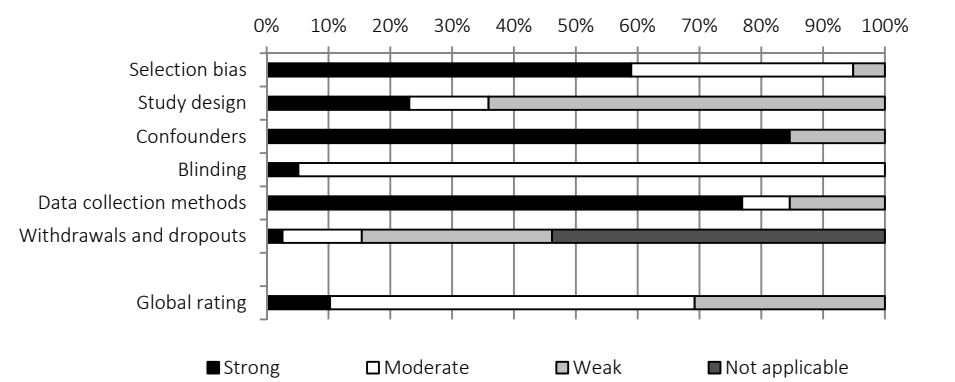


Figure 2 Quality assessment of the 39 included studies using the Quality Assessment Tool for Quantitative Studies [28]. Each study was rated as ‘strong’, ‘moderate’, or ‘weak’ on six individual components. An overall global rating was then assigned to each study with studies classified as ‘strong’ (no weak ratings), ‘moderate’ (one weak rating), or ‘weak’ (two of more weak ratings). The results are averaged per item.

Patient studies

Effect of radiotherapy

Radiologic response - Six studies evaluated any qualitative radiologic response following radiotherapy [33, 40, 42, 48, 51, 52, 66] (Appendix D, 5th column). The definitions of radiological response used in these studies varied widely (Appendix B, 8 - 9th columns); a response not necessarily implicated that re-calcification occurred. Garmatis et al. [40] showed that immediately after radiotherapy (20 - 25 Gy in 8 - 10 fractions) almost 80% of the lesions show a marked improvement. This is in contrast with the trial (10 x 3 Gy vs. 3 x 5 Gy) by Rasmussen et al. [48] who found that, in similarly located bone lesions, at 1 month after radiotherapy about 60% of the lesions had not changed compared to their pre-radiotherapy status. However, at 3 months following radiotherapy the majority of the patients showed a complete or partial response (Appendix B). In addition, after 3 months the largest part of the improvements had already occurred. In other studies [42, 51, 52, 66], response rates ranged from 25% to 76%. It was unclear at what moment in time the data was provided for.

Bone density - Changes in bone density were investigated in seven studies [17, 36-39, 47, 65] (Appendix D, 6th column). All studies showed the same trend: the bone density increased after radiotherapy. Foerster et al. [39] showed in a retrospective study that, in contrast to spinal bone metastases, the bone density in unaffected neighboring vertebral bodies did not change after radiotherapy. Three studies studied the bone density immediately after radiotherapy [17, 37, 65]. Whereas the clinically controlled trial by Koswig and Budach [17] showed that the bone density dropped by 8% (1 x 8 Gy) and 25% (3 x 10 Gy) immediately after radiotherapy, Wachenfeld et al. [65] (18 x 2 Gy) and Crone-Munzebrock et al. [37] (40 - 50 Gy in fractions of 2.5 Gy) did not find this initial drop. Two trials and one cohort study compared single-fraction radiotherapy with multiple-fraction radiotherapy [17, 36, 38]. Koswig et al. [17] and El-Shenshawy et al. [38] both demonstrated a significant increase in bone density after multiple-fraction radiotherapy compared to single-fraction radiotherapy after 6 months (mean: 1 x 8 Gy: 120% vs. 10 x 3 Gy: 173%, $p < 0.001$) and 3 months (post/pre ratio: 1 x 8 Gy: 1.05 vs. 5 x 4 Gy: 1.28 or 10 x 3 Gy: 1.81, $p = 0.049$), respectively. These results were not confirmed by the prospective cohort study by Chow et al. [36], which did not find a significant difference in density change between 1 x 8 Gy, 5 x 4 Gy, and 10 x 3 Gy (post/pre ratio: 1.28 vs. 1.41 vs. 1.45, $p = 0.26$) at 3 months after radiotherapy. McDonald et al. [47] distinguished between lytic and sclerotic lesions. The study showed that bone density in lytic metastases tended to increase, whereas sclerotic lesions tended to demineralize.

Pathological fractures - Eighteen clinical studies reported on fracture rate during follow up after radiotherapy [33-35, 38, 41, 45, 46, 49, 50, 53-59, 61, 62] (Appendix D, 7th column). Overall, fracture rates after primary radiotherapy ranged from 0% to about 15%. In addition, reported rates on progression of spinal fractures after radiotherapy range from about 7% to 55% [50, 58]. Three controlled clinical trials compared single-fraction radiotherapy with multiple-fraction radiotherapy (1 x 8 Gy vs. 10 x 3 Gy [41]; 1 x 8 Gy vs. 5 x 4 Gy or 10 x 3 Gy [38]; 1 x 8 Gy vs. 6 x 4 Gy [57]). While two of these studies observed more pathological fractures after single-fraction radiotherapy than after multiple-fraction radiotherapy (6% vs. 2%, $p = 0.046$ [38]; 4% vs. 2%, $p = <0.05$ [57]), one study did not find a difference in pathological fracture rate (5% vs. 4%, $p =$ not stated [41]). Studies on stereotactic body radiotherapy (SBRT) or stereotactic radiosurgery (SRS) reported fracture rates ranging from approximately 2.5% to 32.5% [33, 34, 46, 55, 56, 61, 62]. In a retrospective matched-pair study, Sohn et al. [56] found two pathological fractures in patients who received SRS and no fractures in patients who received conventional radiotherapy.

Bone density and pathological fractures - The study by El-Shenshawy et al. [38] was the only study that assessed both bone density and fracture rate. A correlation was found between the range of bone density before and three months after radiotherapy and pathological fractures. The density change (ratio of median post/pre radiotherapy) of

patients with a pathological fracture was lower, i.e. 0.78 (range 0.76 - 0.89) than those of patients without a pathological fracture (ratio 1.52 (range 0.67 - 3.42), $p = 0.001$).

Effect of radiotherapy combined with bisphosphonates

Six studies addressed the effect of adding BP to radiotherapy on bone quality [32, 43, 44, 60, 63, 64] (Appendix E). Two retrospective cohort studies [43, 60] compared changes in bone quality between patients receiving only radiotherapy and patients receiving radiotherapy and BPs (ZA). The other four studies comprised a single patient group, which received both radiotherapy and BPs.

Radiologic response - The retrospective cohort study by Kijima et al. [43] showed that the response rate at 6 - 9 months after radiotherapy was significantly higher in patients receiving both radiotherapy and zoledronic acid compared to those receiving only radiotherapy (6/10 vs. 1/13, $p = 0.019$). It must be noted that the point of starting ZA varied from immediately after radiotherapy to 12 months after radiotherapy.

Bone density - Four studies focused on quantitative bone density [39, 44, 63, 64] (Appendix E, 6th column). Of these, three studies consisted of a single intervention group. Although assessed using different methods, all three studies showed an increase in bone density over time after treatment with radiotherapy and disodium pamidronate (DP) or ibandronate (IB). Overall, from 3 months onward the bone density was significantly higher than its pre-radiotherapy value. Vassiliou et al. [64] distinguished between lytic, mixed and sclerotic lesions. Lytic metastases showed the largest changes in bone density, sclerotic lesions the least. Foerster et al. [39] performed a subgroup analysis on patients receiving radiotherapy combined with bisphosphonates versus patients receiving radiotherapy only. In both groups bone density increased over time. In addition, they found that the mean increase in bone density of metastases after 3 months was higher, albeit not significant, in patients receiving radiotherapy and bisphosphonates compared to patients receiving radiotherapy only ($152.59 \text{ HU} \pm 141.99$ vs. $76.03 \text{ HU} \pm 86.6$, $p = 0.069$). After 6 months this effect was less profound ($245.8 \text{ HU} \pm 151.5$ vs. $171.9 \text{ HU} \pm 114.4$, $p = 0.162$).

Pathological fractures - Five studies reported on pathological fractures during follow up [32, 43, 60, 63, 64] (Appendix E, 7th column). Of these, two studies, which were retrospective cohort studies, compared patients treated with radiotherapy with patients treated with radiotherapy and BPs. The first study reported one fracture in the former treatment group and no fractures in the latter group (p not stated) [43]. The second study found three fractures in patients treated with radiotherapy, and two fractures in patients treated with additional BPs (p not stated) [60]. Also, three additional patients (25%) treated with only radiotherapy underwent surgery for impending fractures. Furthermore, one randomized controlled clinical trial investigated the effect of high (10

x 3 Gy) and low (5 x 3 Gy) radiotherapy doses when combined with ZA [32]. Fractures were observed in both the high dose group and in the low dose group (4 vs. 3, p not stated).

Radiologic response and pathological fractures - The study by Kijima et al. [43] was the only study that assessed both radiologic response and fracture rate. However, correlations between radiological response and fracture rate were not reported.

Effect of radiotherapy combined with RANKL inhibitors

None of the included studies addressed the effect of radiotherapy combined with RANKL inhibitors on bone density, bone micro-architecture, bone strength or related outcome parameters.

Discussion

We conducted this study to systematically review all studies on the effect of (1) radiotherapy, (2) radiotherapy combined with bisphosphonates, and (3) radiotherapy combined with RANKL inhibitors on bone quality and bone strength parameters in bone metastases originating from solid tumors.

In clinical practice, patients are often treated with a combination of local radiotherapy and systemic treatments. These systemic treatments include e.g. anticancer treatments with chemotherapy or hormonal therapy, BPs, and RANKL inhibitors. In this systematic review we only focused on BPs and RANKL inhibitors as treatments additional to radiotherapy, as these treatments intend to improve the bone mass. In contrast, other anticancer treatments are primarily used to attack tumor tissue and decrease lesion size. Future research needs to show whether other anticancer therapies have a secondary effect on bone quality and bone strength.

Animal studies were included in this review. Although the translation from pre-clinical animal models to clinical practice is not straightforward, animal studies do have some benefits. Firstly, the experimental designs of animal studies can be very strictly regulated. Moreover, a negative control group (no treatment) can be formulated, which is not always possible in a clinical setting. A negative control enables one to assess the actual effect of e.g. radiotherapy. In addition, outcome measures of interest can be measured directly and more invasive measurements can be conducted. While bone strength in clinical studies needs to be measured indirectly via for example the number of pathological fractures, bone strength in animals can be determined by mechanically loading the bone until failure.

The three included animal studies showed that radiotherapy alone did not foster more new bone formation to restore micro-architecture or biomechanical strength than a negative control. In addition, treatment with radiotherapy did not restore bone quality

and strength to the levels of healthy bones. However, BPs as an adjunct to radiotherapy seemed to be capable of significantly improving trabecular micro-architecture and restoring biomechanical strength to that of normal bone. Thus, based on the identified animal studies there was no evidence that radiotherapy alone leads to re-calcification or an increase in bone strength. It should, however, be noted that only two out of three animal studies determined bone strength and both studies were performed by the same research group. Also, one could argue that a time interval of 9 and 12 weeks is rather early for evaluating ossification. Further research is needed to address these issues.

All studies on the effect of radiotherapy on bone density showed the same trend: bone density increased after radiotherapy. However, there was insufficient evidence to conclude whether or not radiotherapy leads to an improved bone quality and increased bone strength in patients suffering from solid bone metastases. To assess whether radiotherapy indeed improves bone quality and bone strength, radiotherapy treatment should be compared to a negative control. In practice it is, however, difficult to perform studies with a negative control: not treating patients suffering from painful bone metastases might be ethically challenging. A good alternative for formulating a negative control group is comparing different treatment doses of radiotherapy in a randomized controlled trial. Van der Linden et al. evaluated the influence of different treatment schedules on the occurrence of a femoral fracture in 102 patients who participated in a randomized trial on the effectiveness of single-fraction vs. multiple-fraction radiotherapy on pain [67]. The median time to fracturing from the start of radiotherapy was 6 weeks (range 2 - 29) for patients who received single-fraction radiotherapy (1 x 8 Gy) compared to median 17 weeks (range 2 - 35) for the multi-fraction (6 x 4 Gy) patients. Therefore, it was suggested that multi-fraction radiotherapy postponed the occurrence of a pathological fracture in patients with femoral metastases. Based on this finding it can be hypothesized that a higher dose of radiotherapy results in more re-calcification and thus to an improved bone strength than a lower dose of radiotherapy. The current systematic review identified three trials comparing single-fraction radiotherapy with multiple-fraction radiotherapy. The conclusions on differences in fracture rates between single- and multiple-fraction radiotherapy varied between these studies. Previously, two meta-analyses of randomized studies comparing single-fraction *versus* multi-fraction radiotherapy for prevention of bone complications in patients with painful bone metastases were performed. The meta-analysis by Sze et al. [15] reported a higher pathological fracture rate after single-fraction radiotherapy (3.0%; 37/1240) than after multi-fraction radiotherapy (1.6%; 20/1236) (OR 1.82; 95% CI 1.06 - 3.11, $p < 0.05$). This difference was not found in the meta-analysis of Chow and colleagues: 3.2% (65/2018) of the patients developed a pathological fracture in the irradiated region after single-fraction versus 2.8% (57/2004) after multi-fraction radiotherapy (OR 1.10; 95% CI 0.61 - 1.99, $p = 0.75$) [12]. Thus, both the meta-analyses and our study are inconclusive on whether or not multi-fraction radiotherapy is associated with a lower pathological fracture rate than single fraction radiotherapy.

However, the results concerning the studies on fracture rate need to be interpreted with caution. Firstly, most studies were not designed to measure the fracture rate, but studied the effect of radiotherapy on the pain response. Fractures were 'only' noted during follow-up. Intensity and duration of follow-up were very heterogeneous among the several patient studies. The follow-up should be standardized when fracture rates are compared. A longer survival is accompanied with a higher risk of progression of disease and thus with a higher risk of fracture. To the best of our knowledge, there are currently no studies on the effect of radiotherapy dose with fracture rate as the primary outcome measure.

Furthermore, previous research on metastatic femora has shown that axial cortical involvement of the metastatic lesion was the only lesional parameter that was significantly predictive for fracturing [67]. A larger lesion implied a higher risk of fracture. Although more fractures occurred after a single dose of 8 Gy compared to 6 fractions of 4 Gy (23% vs. 7%, $p = 0.02$), Van der Linden et al. did not find the treatment schedule to be predictive for fracturing when correcting for the axial cortical involvement ($p = 0.07$) [67]. Thus, lesion size might be more important than the radiotherapy dose in predicting fracture risk. The studies comparing the effect of single-fraction and multi-fraction radiotherapy on fracture rate included in this systematic review did not correct for lesions size.

In addition, the preexistence of fractures or impending fractures should be taken into account. The exclusion criteria concerning these factors varied across studies included in this systematic review.

When considering changes in bone density, all studies showed the same trend: bone density seemed to increase after treatment with radiotherapy. However, as these studies lacked a control group (no treatment), it cannot be concluded that the increase in bone density was due to the radiotherapy. In addition, co-medication, including BPs, was allowed in most studies. As BPs are known to increase bone density, the observed increase in bone density could also be caused by the BPs. Again, it must be stressed that in practice it is challenging to perform patient studies fulfilling these criteria.

There were discrepancies in the results of papers studying the effect of single-fraction radiotherapy compared with multiple-fraction radiotherapy on bone density. While the studies by Koswig et al. and El-Shenshawy et al. found a higher increase in bone density after multiple-fraction radiotherapy than after single-fraction radiotherapy, Chow et al. did not confirm these findings. In the latter study patients received either 1 x 8 Gy, 5 x 4 Gy, or 10 x 3 Gy and were analyzed as three different groups. In the study by El-Shenshawy et al. patients also received 1 x 8 Gy, 5 x 4 Gy, or 10 x 3 Gy, but patients receiving multiple fractions were analyzed as a single group. In order to draw conclusions, studies should be analyzed in a similar way.

Unfortunately, no correlations between changes in bone density, bone micro-architecture, and bone strength were reported in the animal studies and barely in the patient studies. Therefore, direct correlations between fracture rate and bone density

could not be made on an animal-to animal or patient-to-patient basis. Bone fragility is influenced by bone mass, bone micro-architecture, and tissue quality [68]. An increase in bone mass, i.e. bone density, does not necessarily mean that this newly created bone results in increased bone strength. Thus, fractures can still occur. Without correlating changes in bone mass and fracture rate, no conclusions can be drawn on whether it is the process of re-calcification that leads to improved bone strength or not. Future studies should, therefore, determine both bone quality and bone strength or fracture rate within the same animal or patient.

The combination of BPs and radiotherapy showed an increase in bone density in metastatic bone lesions in all included studies. However, the number and quality of studies that actually compared radiotherapy + BP treatment with radiotherapy treatment was limited. Although the included patient studies that compared radiotherapy + BP treatment with radiotherapy seem to show a positive effect of adjunct BPs on bone quality, this was not significantly different [39, 43, 60]. Therefore, there was insufficient evidence to draw any firm conclusions on the additional effect of BPs. Several animal studies, however, showed positive effects of BPs as adjunct therapy in increasing bone stability [29, 30]. Although challenging, we therefore recommend performing randomized patient studies of good methodological quality to investigate the adjunct effect of BPs. Recently, Hoskin et al. evaluated the effect of ibandronate vs. single-fraction radiotherapy (1 x 8 Gy) on the occurrence of a pathological fracture in 470 patients participating in a randomized controlled trial focusing on pain [69]. They did not find a statistical difference in the occurrence of a pathological fracture (ibandronate: 7 (3%) vs. radiotherapy: 5 (2%), $p = 0.31$), suggesting equal effectiveness of ibandronate and radiotherapy on improving bone strength.

Similarly, this systematic review showed that neither animal nor patient studies have been performed on the effect of radiotherapy combined with RANKL inhibitors on bone quality and bone strength. Recent studies showed that RANKL inhibitors, i.e. Denosumab, are more effective in preventing skeletal related events than bisphosphonates [70-72]. Therefore, it would be valuable to investigate the possible additive effect of RANKL inhibitors with radiotherapy over BPs with radiotherapy. Animal studies might be suitable to provide a first estimation on this effect.

Although this review provides an overview of the effects of radiotherapy, BPs and RANKL inhibitors in a systematic manner, there are several limitations to consider. Firstly, the majority of included studies lack a control group. Therefore, the effects found in these studies could not be attributed with certainty to the treatment given. Randomized controlled trials are needed to establish whether radiotherapy alone increases bone stability and whether BPs or RANKL inhibitors have an additive effect on improving bone quality and bone strength.

In addition, there was a lot of variation between studies in terms of measuring the radiological response and bone density. In the eight studies reporting on radiologic response seven unique definitions were used for radiologic response; in eight studies

reporting on bone density three different methods were used. The use of different methods and definitions complicates comparison of results between studies. Therefore, it would be beneficial if such outcome measures would be standardized, as has been done for pain scores.

Moreover, as stated above, most patient studies were not designed to measure fracture rates, but studied the pain response after radiotherapy. Fractures were noted during follow-up. To be able to assess the actual effect of radiotherapy on fracture risk, studies should be designed with fracture rate as the primary outcome measure. In addition, all factors affecting the fracture risk, such as lesion size, preexisting or impending fractures, and perhaps also the load applied to the skeleton during physical activities, should be taken into account in the study design.

The final point of concern is the quality of the included papers. Only four studies were evaluated as 'strong'. Of these, one is an animal study [30], two are controlled clinical trials comparing the effect of multi- *versus* multiple-fraction radiotherapy [41, 57], and one is cohort study investigating the changes in bone density after radiotherapy + BP treatment [63]. When focusing on the good quality papers only, still no firm conclusions on the effect of radiotherapy, BPs and RANKL inhibitors on bone quality and bone strength can be drawn, as (1) the controlled clinical trials were not designed to measure fracture rate, (2) the results of the controlled clinical trials are inconclusive and (3) the only study on BPs lacks a control group.

Although the clinical experience of many clinicians is that radiotherapy strengthens bones due to re-calcification in a large proportion of patients, this is not supported by this systematic review. This discrepancy may be explained by the fact that our literature search identified no large prospective, controlled patient studies primarily looking at re-calcification or fracture rate. Also, the studies that were included in this review employed different definitions of similar outcome measures and used different methods to quantify them. This might have resulted in the inability to identify changes in bone quality and fracture rate after radiotherapy. However, it could also be questioned whether the changes seen on X-rays or CT images indeed reflect the appearance of newly formed bone that is of sufficient quality to improved bone strength.

In this systematic review we obtained a biomechanical approach and focused on changes in bone density and pathological fractures. In clinical practice, however, radiotherapy may not only be administered to prevent pathological fractures, but also for metastatic cord compression (MSCC) and pain. Previous studies have shown that the addition of zoledronic acid to radiotherapy improved local control and overall control of MSCC in patients irradiated for this complication in bone metastases [73]. In addition, a study showed that more vertebrae were stable after radiotherapy than before treatment [54]. Therefore, in order to fully evaluate the effectiveness of radiotherapy, with or without bisphosphonates or RANKL inhibitors, a broad spectrum of outcome parameters should be considered. Based on our systematic review, however, we only conclude that there is a lack of evidence that radiotherapy, with or without

bisphosphonates or RANKL inhibitors, increases bone density and prevents pathological fractures.

Conclusion

Based on this systematic review, it can be concluded there was no sufficient evidence that radiotherapy had a positive effect on bone quality and fracture risk. In addition, animal studies showed that the addition of BPs to radiotherapy restored bone quality and bone strength to that of healthy bone, whereas this is not yet proven in patients. Furthermore, there were neither animal nor patient studies addressing the effect of RANKL inhibitors as an adjunct to radiotherapy on bone quality and bone strength.

Acknowledgments

We greatly appreciate the help of Elmie Peters and Alice Tillema from the Radboud University Nijmegen Library of Medical Sciences with developing the search strategy.

Appendices

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.radonc.2016.03.001>.

References

1. Coleman RE. Metastatic bone disease: clinical features, pathophysiology and treatment strategies. *Cancer Treat Rev* 2001;27(3):165-176.
2. Coleman RE. Skeletal complications of malignancy. *Cancer* 1997;80(8 Suppl):1588-1594.
3. Gralow J, Tripathy D. Managing metastatic bone pain: the role of bisphosphonates. *J Pain Symptom Manage* 2007;33(4):462-472.
4. Costa L, Badia X, Chow E, Lipton A, Wardley A. Impact of skeletal complications on patients' quality of life, mobility, and functional independence. *Support Care Cancer* 2008;16(8):879-889.
5. Falkmer U, Jarhult J, Wersall P, Cavallin-Stahl E. A systematic overview of radiation therapy effects in skeletal metastases. *Acta Oncol* 2003;42(5-6):620-633.
6. Van der Linden YM, Dijkstra PD, Kroon HM, Lok JJ, Noordijk EM, Leer JW, Marijnen CA. Comparative analysis of risk factors for pathological fracture with femoral metastases. *J Bone Joint Surg Br* 2004;86(4):566-573.
7. Bartels RH, van der Linden YM, van der Graaf WT. Spinal extradural metastasis: review of current treatment options. *CA Cancer J Clin* 2008;58(4):245-259.
8. Fisher CG, DiPaola CP, Ryken TC, Bilsky MH, Shaffrey CI, Berven SH, Harrop JS, Fehlings MG, Boriani S, Chou D, Schmidt MH, Polly DW, Biagini R, Burch S, Dekutoski MB, Ganju A, Gerszten PC, Gokaslan ZL, Groff MW, Liebsch NJ, Mendel E, Okuno SH, Patel S, Rhines LD, Rose PS, Sciubba DM, Sundaresan N, Tomita K, Varga PP, Vialle LR, Vrionis FD, Yamada Y, Fourny DR. A novel classification system for spinal instability in neoplastic disease: an evidence-based approach and expert consensus from the Spine Oncology Study Group. *Spine (Phila Pa 1976)* 2010;35(22):E1221-1229.
9. Nielsen OS, Munro AJ, Tannock IF. Bone metastases: pathophysiology and management policy. *J Clin Oncol* 1991;9(3):509-524.
10. Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. *BMJ* 1996;312(7041):1254-1259.
11. Unnanuntana A, Gladnick BP, Donnelly E, Lane JM. The assessment of fracture risk. *J Bone Joint Surg Am* 2010;92(3):743-753.
12. Chow E, Harris K, Fan G, Tsao M, Sze WM. Palliative radiotherapy trials for bone metastases: a systematic review. *J Clin Oncol* 2007;25(11):1423-1436.
13. Chow E, van der Linden YM, Roos D, Hartsell WF, Hoskin P, Wu JS, Brundage MD, Nabid A, Tissing-Tan CJ, Oei B, Babington S, Demas WF, Wilson CF, Meyer RM, Chen BE, Wong RK. Single versus multiple fractions of repeat radiation for painful bone metastases: a randomised, controlled, non-inferiority trial. *Lancet Oncol* 2014;15(2):164-171.
14. Maranzano E, Trippa F, Casale M, Costantini S, Lupattelli M, Bellavita R, Marafioti L, Pergolizzi S, Santacaterina A, Mignogna M, Silvano G, Fusco V. 8Gy single-dose radiotherapy is effective in metastatic spinal cord compression: results of a phase III randomized multicentre Italian trial. *Radiother Oncol* 2009;93(2):174-179.
15. Sze WM, Shelley M, Held I, Mason M. Palliation of metastatic bone pain: single fraction versus multifraction radiotherapy - a systematic review of the randomised trials. *Cochrane Database Syst Rev* 2004(2):CD004721.
16. Wu JS, Wong R, Johnston M, Bezjak A, Whelan T, Cancer Care Ontario Practice Guidelines Initiative Supportive Care G. Meta-analysis of dose-fractionation radiotherapy trials for the palliation of painful bone metastases. *Int J Radiat Oncol Biol Phys* 2003;55(3):594-605.
17. Koswig S, Budach V. [Remineralization and pain relief in bone metastases after after different radiotherapy fractions (10 times 3 Gy vs. 1 time 8 Gy). A prospective study]. *Strahlenther Onkol* 1999;175(10):500-508.
18. Lopez-Olivo MA, Shah NA, Pratt G, Risser JM, Symanski E, Suarez-Almazor ME. Bisphosphonates in the treatment of patients with lung cancer and metastatic bone disease: a systematic review and meta-analysis. *Support Care Cancer* 2012;20(11):2985-2998.
19. Machado M, Cruz LS, Tannus G, Fonseca M. Efficacy of clodronate, pamidronate, and zoledronate in reducing morbidity and mortality in cancer patients with bone metastasis: a meta-analysis of randomized clinical trials. *Clin Ther* 2009;31(5):962-979.
20. Pavlakis N, Schmidt R, Stockler M. Bisphosphonates for breast cancer. *Cochrane Database Syst Rev* 2005(3):CD003474.

21. Yuen KK, Shelley M, Sze WM, Wilt T, Mason MD. Bisphosphonates for advanced prostate cancer. *Cochrane Database Syst Rev* 2006(4):CD006250.
22. Boyle WJ, Simonet WS, Lacey DL. Osteoclast differentiation and activation. *Nat New Biol* 2003;423(6937):337-342.
23. Rades D, Schild SE, Abrahm JL. Treatment of painful bone metastases. *Nat Rev Clin Oncol* 2010;7(4):220-229.
24. Baron R, Ferrari S, Russell RG. Denosumab and bisphosphonates: different mechanisms of action and effects. *Bone* 2011;48(4):677-692.
25. Drake MT, Clarke BL, Khosla S. Bisphosphonates: mechanism of action and role in clinical practice. *Mayo Clin Proc* 2008;83(9):1032-1045.
26. Epstein MS, Ephros HD, Epstein JB. Review of current literature and implications of RANKL inhibitors for oral health care providers. *Oral surgery, oral medicine, oral pathology and oral radiology* 2013;116(6):e437-442.
27. Hoskin PJ. Bisphosphonates and radiation therapy for palliation of metastatic bone disease. *Cancer Treat Rev* 2003;29(4):321-327.
28. Effective Public Health Practice Project. Quality Assessment Tool for Quantitative Studies. Last accessed 2015 February 20. Available from: http://www.ehphp.ca/PDF/Quality%20Assessment%20Tool_2010_2.pdf
29. Arrington SA, Damron TA, Mann KA, Allen MJ. Concurrent administration of zoledronic acid and irradiation leads to improved bone density, biomechanical strength, and microarchitecture in a mouse model of tumor-induced osteolysis. *J Surg Oncol* 2008;97(3):284-290.
30. Arrington SA, Fisher ER, Willick GE, Mann KA, Allen MJ. Anabolic and antiresorptive drugs improve trabecular microarchitecture and reduce fracture risk following radiation therapy. *Calcif Tissue Int* 2010;87(3):263-272.
31. Krempien R, Huber PE, Harms W, Treiber M, Wannemacher M, Krempien B. Combination of early bisphosphonate administration and irradiation leads to improved remineralization and restabilization of osteolytic bone metastases in an animal tumor model. *Cancer* 2003;98(6):1318-1324.
32. Atahan L, Yildiz F, Cengiz M, Kaplan B, Ozkan M, Yazici G, Gundog M, Haydaroglu A, Korcum AF, Sengoz M, Dincer M, Akmansu M, Engin K, Hayran M. Zoledronic acid concurrent with either high- or reduced-dose palliative radiotherapy in the management of the breast cancer patients with bone metastases: a phase IV randomized clinical study. *Support Care Cancer* 2010;18(6):691-698.
33. Balagamwala EH, Angelov L, Koyfman SA, Suh JH, Reddy CA, Djemil T, Hunter GK, Xia P, Chao ST. Single-fraction stereotactic body radiotherapy for spinal metastases from renal cell carcinoma. *J Neurosurg Spine* 2012;17(6):556-564.
34. Chang UK, Kim MS, Han CJ, Lee DH. Clinical result of stereotactic radiosurgery for spinal metastasis from hepatocellular carcinoma: comparison with conventional radiation therapy. *J Neurooncol* 2014;119(1):141-148.
35. Cheng DS, Seitz CB, Eyre HJ. Nonoperative management of femoral, humeral, and acetabular metastases in patients with breast carcinoma. *Cancer* 1980;45(7):1533-1537.
36. Chow E, Holden L, Rubenstein J, Christakis M, Sixel K, Vidmar M, Finkelstein J, Hayter C, Loblaw A, Wong R, Szumacher E, Danjoux C. Computed tomography (CT) evaluation of breast cancer patients with osteolytic bone metastases undergoing palliative radiotherapy--a feasibility study. *Radiother Oncol* 2004;70(3):291-294.
37. Crone-Munzebrock W, Spielmann RP, Brockmann WP. [Clinical studies of the quantitative changes in mineral salt content of irradiated vertebral body metastases with 2-energy computerized tomography]. *Rontgenblätter* 1988;41(6):223-228.
38. El-Shenshawy HM, Kandeel A, El-Essawy S. The effect of a single fraction compared to multiple fractions radiotherapy on painful bone metastases with evaluation of computed tomography bone density in osteolytic bone metastases. *Bull Alex Fac Med* 2006;42(2):389-391.
39. Foerster R, Eisele C, Bruckner T, Bostel T, Schlampp I, Wolf R, Debus J, Rief H. Bone density as a marker for local response to radiotherapy of spinal bone metastases in women with breast cancer: a retrospective analysis. *Radiat Oncol* 2015;10:62.
40. Garmatis CJ, Chu FC. The effectiveness of radiation therapy in the treatment of bone metastases from breast cancer. *Radiology* 1978;126(1):235-237.

41. Hartsell WF, Scott CB, Bruner DW, Scarantino CW, Ivker RA, Roach M, 3rd, Suh JH, Demas WF, Movsas B, Petersen IA, Konski AA, Cleeland CS, Janjan NA, DeSilvio M. Randomized trial of short- versus long-course radiotherapy for palliation of painful bone metastases. *J Natl Cancer Inst* 2005;97(11):798-804.
42. Huber S, Ulsperger E, Gomar C, Koderhold G, Czemberek H. Osseous metastases in breast cancer: radiographic monitoring of therapeutic response. *Anticancer Res* 2002;22(2B):1279-1288.
43. Kijima T, Fujii Y, Suyama T, Okubo Y, Yamamoto S, Masuda H, Yonese J, Fukui I. Radiotherapy to bone metastases from renal cell carcinoma with or without zoledronate. *BJU Int* 2009;103(5):620-624.
44. Kouloulas V, Matsopoulos G, Kouvaris J, Dardoufas C, Bottomley A, Varela M, Uzunoglu N, Antypas C, Metafa A, Mouloupoulos A, Sandilos P, Vlahos L. Radiotherapy in conjunction with intravenous infusion of 180 mg of disodium pamidronate in management of osteolytic metastases from breast cancer: clinical evaluation, biochemical markers, quality of life, and monitoring of recalcification using assessments of gray-level histogram in plain radiographs. *Int J Radiat Oncol Biol Phys* 2003;57(1):143-157.
45. Lee DS, Kwak YK, Jeong SM, Song JH, Kang YN, Lee SN, Jang HS, Kim YS, Yoon SC, Choi BO. High-dose radiotherapy using helical tomotherapy for vertebral metastasis: early clinical outcomes and cord dose specification. *Jpn J Clin Oncol* 2013;43(6):646-653.
46. Lee E, Kim TG, Park HC, Yu JI, Lim do H, Nam H, Lee H, Lee JH. Clinical outcomes of stereotactic body radiotherapy for spinal metastases from hepatocellular carcinoma. *Radiation oncology journal* 2015;33(3):217-225.
47. McDonald R, Probyn L, Poon I, Erler D, Brotherston D, Soliman H, Cheung P, Chung H, Chu W, Loblaw A, Thavarajah N, Lang C, Chin L, Chow E, Sahgal A. Computed Tomography Evaluation of Density Following Stereotactic Body Radiation Therapy of Nonspine Bone Metastases. *Technol Cancer Res Treat* 2015.
48. Rasmussen B, Vejborg I, Jensen AB, Andersson M, Banning AM, Hoffmann T, Pfeiffer P, Nielsen HK, Sjogren P. Irradiation of bone metastases in breast cancer patients: a randomized study with 1 year follow-up. *Radiother Oncol* 1995;34(3):179-184.
49. Reichel LM, Pohar S, Heiner J, Buzaianu EM, Damron TA. Radiotherapy to bone has utility in multifocal metastatic renal carcinoma. *Clin Orthop Relat Res* 2007;459:133-138.
50. Rhee WJ, Kim KH, Chang JS, Kim HJ, Choi S, Koom WS. Vertebral compression fractures after spine irradiation using conventional fractionation in patients with metastatic colorectal cancer. *Radiation oncology journal* 2014;32(4):221-230.
51. Rieden K, Mende U, Adolph J, zum Winkel K. [Accelerated irradiation of bone metastases]. *Strahlenther Onkol* 1989a;165(1):23-27.
52. Rieden K, Adolph J, Lellig U, zum Winkel K. [The radiotherapeutic effect on bone metastases in relation to the frequency of metastases, sites of metastases and histology of the primary tumor]. *Strahlenther Onkol* 1989b;165(5):380-385.
53. Rief H, Bischof M, Bruckner T, Welzel T, Askoxylakis V, Rieken S, Lindel K, Combs S, Debus J. The stability of osseous metastases of the spine in lung cancer - a retrospective analysis of 338 cases. *Radiat Oncol* 2013;8(1):200.
54. Schlamp I, Rieken S, Habermehl D, Bruckner T, Forster R, Debus J, Rief H. Stability of spinal bone metastases in breast cancer after radiotherapy: a retrospective analysis of 157 cases. *Strahlenther Onkol* 2014;190(9):792-797.
55. Sellin JN, Reichardt W, Bishop AJ, Suki D, Rhines LD, Settle SH, Brown PD, Li J, Rao G, Chang EL, Tatsui CE. Factors affecting survival in 37 consecutive patients undergoing de novo stereotactic radiosurgery for contiguous sites of vertebral body metastasis from renal cell carcinoma. *J Neurosurg Spine* 2015;22(1):52-59.
56. Sohn S, Chung CK, Sohn MJ, Chang UK, Kim SH, Kim J, Park E. Stereotactic radiosurgery compared with external radiation therapy as a primary treatment in spine metastasis from renal cell carcinoma: a multicenter, matched-pair study. *J Neurooncol* 2014;119(1):121-128.
57. Steenland E, Leer JW, van Houwelingen H, Post WJ, van den Hout WB, Kievit J, de Haes H, Martijn H, Oei B, Vonk E, van der Steen-Banasik E, Wiggensraad RG, Hoogenhout J, Warlam-Rodenhuis C, van Tienhoven G, Wanders R, Pomp J, van Reijn M, van Mierlo I, Rutten E. The effect of a single fraction compared to multiple fractions on painful bone metastases: a global analysis of the Dutch Bone Metastasis Study. *Radiother Oncol* 1999;52(2):101-109.
58. Switlyk MD, Bruland OS, Skjeldal S, Hald JK, Seierstad T, Zaikova O. Radiotherapy for spinal metastases from breast cancer with emphasis on local disease control and pain response using repeated MRI. *Journal of Bone Oncology* 2014;3(1):5-9.

59. Tabata K, Niibe Y, Satoh T, Tsumura H, Ikeda M, Minamida S, Fujita T, Ishii D, Iwamura M, Hayakawa K, Baba S. Radiotherapy for oligometastases and oligo-recurrence of bone in prostate cancer. *Pulm Med* 2012;2012:541656.
60. Takeda N, Isu K, Hiraga H, Shinohara N, Minami A, Kamata H. Zoledronic acid enhances the effect of radiotherapy for bone metastases from renal cell carcinomas: more than a 24-month median follow-up. *J Orthop Sci* 2012;17(6):770-774.
61. Thibault I, Al-Omair A, Masucci GL, Masson-Cote L, Lochray F, Korol R, Cheng L, Xu W, Yee A, Fehlings MG, Bjarnason GA, Sahgal A. Spine stereotactic body radiotherapy for renal cell cancer spinal metastases: analysis of outcomes and risk of vertebral compression fracture. *J Neurosurg Spine* 2014;21(5):711-718.
62. Ursino S, Montrone S, Cantarella M, Menghini V, Matteucci F, Mazzotti V, Fiorica F, Fedele D, Erba P, Morganti R, Fabrini MG, Caramella D. Stereotactic body radiotherapy of bone metastases in oligometastatic disease: prognostic factors of oncologic outcomes. *Tumori* 2015;0(0):0.
63. Vassiliou V, Kalogeropoulou C, Christopoulos C, Solomou E, Leotsinides M, Kardamakis D. Combination ibandronate and radiotherapy for the treatment of bone metastases: clinical evaluation and radiologic assessment. *Int J Radiat Oncol Biol Phys* 2007a;67(1):264-272.
64. Vassiliou V, Kalogeropoulou C, Giannopoulou E, Leotsinidis M, Tsota I, Kardamakis D. A novel study investigating the therapeutic outcome of patients with lytic, mixed and sclerotic bone metastases treated with combined radiotherapy and ibandronate. *Clin Exp Metastasis* 2007b;24(3):169-178.
65. Wachenfeld I, Sanner G, Bottcher HD, Kollath J. [The remineralization of the vertebral metastases of breast carcinoma after radiotherapy]. *Strahlenther Onkol* 1996;172(6):332-341.
66. Wagner W. [Radiotherapy of osseous metastases in breast cancer]. *Geburtshilfe Frauenheilkd* 1991;51(2):106-108.
67. van der Linden YM, Kroon HM, Dijkstra SP, Lok JJ, Noordijk EM, Leer JW, Marijn CA, Dutch Bone Metastasis Study G. Simple radiographic parameter predicts fracturing in metastatic femoral bone lesions: results from a randomised trial. *Radiother Oncol* 2003;69(1):21-31.
68. Turner CH. Biomechanics of bone: determinants of skeletal fragility and bone quality. *Osteoporos Int* 2002;13(2):97-104.
69. Hoskin P, Sundar S, Reczko K, Forsyth S, Mithal N, Sizer B, Bloomfield D, Upadhyay S, Wilson P, Kirkwood A, Stratford M, Jitlal M, Hackshaw A. A Multicenter Randomized Trial of Ibandronate Compared With Single-Dose Radiotherapy for Localized Metastatic Bone Pain in Prostate Cancer. *J Natl Cancer Inst* 2015;107(10).
70. Fizazi K, Carducci M, Smith M, Damiao R, Brown J, Karsh L, Milecki P, Shore N, Rader M, Wang H, Jiang Q, Tadros S, Dansey R, Goessl C. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. *Lancet* 2011;377(9768):813-822.
71. Lipton A, Fizazi K, Stopeck AT, Henry DH, Brown JE, Yardley DA, Richardson GE, Siena S, Maroto P, Clemens M, Bilynsky B, Charu V, Beuzeboc P, Rader M, Viniegra M, Saad F, Ke C, Braun A, Jun S. Superiority of denosumab to zoledronic acid for prevention of skeletal-related events: a combined analysis of 3 pivotal, randomised, phase 3 trials. *Eur J Cancer* 2012;48(16):3082-3092.
72. Stopeck AT, Lipton A, Body JJ, Steger GG, Tonkin K, de Boer RH, Lichinitser M, Fujiwara Y, Yardley DA, Viniegra M, Fan M, Jiang Q, Dansey R, Jun S, Braun A. Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer: a randomized, double-blind study. *J Clin Oncol* 2010;28(35):5132-5139.
73. Rades D, Hakim SG, Bajrovic A, Karstens JH, Veninga T, Rudat V, Schild SE. Impact of zoledronic acid on control of metastatic spinal cord compression. *Strahlenther Onkol* 2012;188(10):910-916.



9

General discussion and future perspectives

Estimating spinal stability or instability and, hence, the risk of (further) vertebral deformation and progressive complaints, such as pain and neurological deficits, plays an important role in the process of treatment decision making in patients with cancer and spinal bone metastases. The majority of patients with painful but stable spines can effectively be treated with non-invasive radiotherapy, whereas a selection of patients with present or impending spinal instability might gain from additional surgical stabilization. However, the assessment of spinal stability is challenging and is currently mostly done by treating physicians relying on their clinical experience. The goal of this work was to improve the assessment of spinal (in)stability in patients suffering from spinal bone metastases, and, as a consequence, the multidisciplinary care for these patients. This chapter reflects on the work described in this thesis and outlines future perspectives related to the findings in this thesis.

Defining spinal instability

The main aim of this thesis was to improve the assessment of spinal (in)stability in metastatic spinal bone disease. This required a clear definition of the term spinal instability with reference to metastatic bone disease. For the purposes of clinical decision making and research, the Spine Oncology Study Group (SOSG) defined neoplastic spinal instability as ‘loss of spinal integrity as a result of a neoplastic process that is associated with movement-related pain, symptomatic or progressive deformity, and/or neural compromise under physiologic loads’ [1]. Subsequently, the SOSG proposed a clinical scoring system to help physicians to gain insight into the degree of spinal instability: the Spinal Instability Neoplastic Score (SINS). Of note, the SOSG and the modified Delphi technique used to develop the SINS were dominated by surgical physicians, whereas the vast majority of patients with spinal bone metastases is treated by radiation oncologists. Therefore, the clinical experience regarding the ‘natural course of disease’ without surgery might have been suboptimal and their opinions might have been biased towards the need for surgical procedures.

Despite the seemingly clear definition of spinal instability set by the SOSG, its interpretation is not clear-cut. The ambiguity of this definition is reflected in the broad variety of outcome measures used in studies investigating the association between SINS scores and the development or progression of spinal instability after treatment of patients with cancer and spinal bone metastases. In **Chapter 3** we used the occurrence of adverse events as outcome measures for indicating spinal instability. Adverse events indicating the presence of spinal instability were, in our study, postulated as (1) development of a new fracture; (2) progression of an existing pathological fracture; and (3) deterioration of alignment requiring surgical stabilization. Similarly, Cunha et al. [2], Germano et al. [3], Lee et al. [4], and Sahgal et al. [5] defined adverse events as radiographic (1) *de novo* vertebral compression fractures or (2) fracture progression. In contrast, Lam et al. [6] adopted a much broader definition of an event, and defined

clinically significant adverse events as follows: (1) symptomatic vertebral body fracture; (2) hospitalization resulting from uncontrolled pain at the previously irradiated spine site; (3) interventional procedures for pain control at the spine; (4) salvage spinal surgery; (5) any new or deterioration in neurologic symptoms; or (6) cord or cauda equina compression. Furthermore, Aiba et al. [7] considered the time from diagnosis of bone metastasis to the occurrence of skeletal related events (SREs) as primary outcome, with SREs defined as (1) spinal compression; (2) pathological fracture; (3) spinal surgery; or (4) hypercalcemia. Thus, whereas all these studies aimed to evaluate the prognostic value of the SINS classification system following the same definition, the interpretations of, and measures for, spinal instability differed considerably. Due to this diversity, comparing the results and conclusions of studies addressing similar research questions is very difficult and they should not automatically be put on par.

The use of the Spinal Instability Neoplastic Score for assessing spinal instability

Chapter 3 describes a retrospective cohort study to evaluate the predictive value of the SINS system in patients with symptomatic spinal bone metastases treated with radiotherapy. It was shown that the total SINS classification was not significantly associated with spinal instability, measured using the occurrence of adverse events (development of a new fracture; progression of an existing pathological fracture; or deterioration of alignment requiring surgical stabilization) within the studied population. Of the individual components, only 'location' showed to be significant, but had a protective effect rather than a harmful effect, as implied by the SINS. Therefore, we concluded that the clinical applicability of the SINS as a tool to assess spinal instability seemed, in its current form, limited.

In this study we excluded a selection of patients who had evident clinical spinal instability and were operated on. One could argue that including only patients treated with radiotherapy has resulted in major selection bias. However, we feel that especially in this patient group, in which a limited risk of spinal instability is expected, it is of utmost importance to identify those patients who, after radiotherapy, underwent an event and perhaps would have gained in terms of sustaining quality of life if a surgical stabilizing procedure had been performed before administration of radiotherapy. Therefore, by leaving out patients who were primary stabilized, we focused on this clinically important group in which there is some clinical equipoise. Hence, excluding patients who were operated on did not introduce major selection bias.

From an ethical point of view, debilitating complications such as progressive pain and neurological problems should be prevented and patients should be referred for surgery if needed. Consequently, one will never know whether spinal instability would have occurred if the vertebra had not been treated surgically. Thus, the SINS score cannot be evaluated in the full population of patients with spinal bone metastases. Alternatively, one could, in a research setting, determine the SINS score of patients who

have been referred for surgery, and to evaluate whether different treatment decisions would have been made based on knowledge of the SINS score. In fact, Versteeg et al. [8] determined the SINS based on pre-treatment imaging for patients with spinal bone metastases treated with palliative surgery or radiotherapy between 2009 and 2013. The SINS was introduced in the institutions concerned mid-2011. SINS scores for the surgery and radiotherapy group were determined for the period before and after introduction of the SINS. It was shown that the SINS was significantly higher in the surgical group than in the radiotherapy group and that the introduction of the SINS led to a decrease in mean SINS score for both groups. The latter was caused by more patients with a score of potential spinal instability and an indication for surgical stabilization being operated on after introduction of the SINS. These findings might suggest that using SINS in metastatic spinal bone disease increases awareness for instability and could subsequently result in earlier and more appropriate referrals for surgical intervention. However, the trade-off between clinical gain of (prophylactic) (minimally invasive) surgical procedures against the impact of invasive procedures on the patient's condition has to be proven in further studies.

Similar to the retrospective patient study described in **Chapter 3**, the evidence-based Dutch national guideline on metastases and hematological malignancies located within the spine also advised against the use of the SINS as predictor for spinal instability (**Chapter 2**). The main arguments for this advice were the reported contradicting findings on the levels of inter- and intra-observer agreement, and, more importantly, the lack of validation of the SINS's predictive power to discriminate between lesions at risk and not at risk of progressive debilitating instability in a prospective setting. Nevertheless, **Chapters 2 and 3** state that the SINS can be useful as tool for streamlining communication between physicians of different medical specialties and for facilitating decision making concerning surgical consultation.

Multidisciplinary consultation (MC) meetings could also aid in gaining knowledge on spinal instability and on the use of the SINS in patients with spinal bone metastases. In such meetings, spine experts representing the different disciplines involved determine whether or not a patient presents with (impending) instability. Although the majority of the patients is neurologically intact at presentation, some of them develop neurological deficits in future. Ideally, the patients' actual follow-up also will be discussed in MC meetings, as this provides valuable feedback on the assessment of spinal (in)stability and treatment decisions previously made.

Moreover, the studies described in **Chapters 2 and 3** suggest that validation in a prospective setting is a prerequisite for providing a more definite answer on the SINS's predictive power to discriminate between lesions at risk and not at risk of progressive debilitating instability. Such a prospective validation is currently lacking. The main benefit of a prospective study compared to a retrospective approach is that the data collection can be especially designed for the research aim as well as performed in a highly standardized manner. This is beneficial in several ways. Firstly, medical imaging

can not only be collected at specific time intervals, but also with the optimal settings for evaluation of bone tissue integrity. In addition, prospective and standardized data collection is especially beneficial in recording patient related factors such as pain scores, quality of life items, and neurological problems, for which retrospective studies need to rely on incomplete notes in the patients' medical charts. In future, therefore, a large prospective cohort of patients with cancer and spinal bone metastases, receiving care as usual, should be generated. The pre-treatment SINS scores as well as the follow-up of patients after radiotherapy and surgery, although difficult, should be collected. Subsequently, it can be evaluated, in a prospective setting, whether the SINS is predictive for spinal instability or not.

Finite element models as an additive method for assessing spinal instability

In **Chapters 4, 5, 6, and 7** we adopted an alternative approach to assess spinal instability and used engineering measurements of stiffness and strength as an indicator. In previous experimental as well as finite element (FE) research, measurements of stiffness, strength, burst fracture initiation, and canal compromise have often been used to identify risk factors for bone strength or spinal instability [9-17]. Risk factors for limited stiffness or bone strength are, however, not necessarily interchangeable with risk factors for spinal instability in the clinical context, as the engineering measurements focus on (local) bony deformation and leave out clinical aspects. Nevertheless, instability due to bony deformation could be an essential step for developing clinical symptoms.

Finite element models calculate bone strength using case-specific geometrical and material parameters, thereby not only accounting for parameters related to lesion and patient, but also covering additional aspects that affect the fracture risk, such as the initial strength of the bone and the daily loads applied to the bone. Within our Orthopaedic Research Laboratory a workflow to generate case-specific FE models for assessing bone strength in metastatically affected femora has been developed. These femoral FE models have not only shown to accurately predict femoral strength *in vitro* [18], but were also able to distinguish between patients who did and did not sustain a pathological femoral fracture after radiotherapy [19]. Given these promising results, the workflow developed for the femur was applied to the spine, as described in this thesis.

Whereas previous spinal FE models predicting failure behavior included single vertebrae [20-31], a more realistic biomechanical environment of the vertebrae under investigation is created by using 3-segment spinal units, which consist of three consecutive vertebrae and two intervertebral discs (IVDs). In this way, the (middle) target vertebra is loaded via two IVDs, the posterior elements, and the spinal ligaments, thereby transferring load as would happen under *in vivo* conditions. Using 3-segment spinal units, however, makes *in vitro* experiments and FE simulations more complex.

The validation of the FE model started with an experimental study in which 16 3-segment spinal units with and without simulated metastases were destructively tested in

axial compression (**Chapter 4**). We subsequently used these experiments in a ranking study, in which we assessed how accurate experienced clinicians of different clinical specialties were at predicting the strength of vertebrae with simulated metastatic lesions (**Chapter 5**). Interestingly, next to large variations between clinicians, we saw that clinicians performed inconsistently in repeated ranking tasks, even though they had the same imaging information at their disposal. Therefore, this ranking study stressed the urge for an objective protocol or method to assess vertebral strength. The FE models generated in **Chapter 6** were able to correctly indicate which vertebrae failed during the experiments, but had difficulties predicting the 3D deformation of the failed vertebra, particularly in case of endplate failure. Furthermore, the FE model could strongly predict stiffness, but only weakly predicted vertebral bone strength. Consequently, the current FE model requires substantial improvements before it can be defined as being experimentally validated, and before its predictive capacity can be tested in a patient population (clinical validation).

As a first future clinical validation step, one could, for example, generate FE models for patients treated with radiotherapy while registering the SINS score. By, subsequently, comparing the patient's actual follow-up with the FE-determined bone strength, one could investigate whether patients with an adverse event had a lower bone strength before treatment than patients without an adverse event. If so, FE models might be able to aid in identifying patients at risk for developing adverse events and, hence, guide in choosing optimal treatment strategies. Alternatively, it would also be valuable to assess FE-determined bone strength in patients who were operated on while registering the SINS score. It is interesting to evaluate whether all these patients had a low bone strength before surgery, or whether a subgroup with a high pre-treatment bone strength could be identified, thus withholding patients from undergoing potentially unnecessary surgery, and preventing overtreatment. In general, it would also be interesting to assess the relationship between SINS score and FE predicted bone strength.

Our attempt to more realistically simulate vertebral failure by using 3-segment spinal units seems, for now, not yet sufficient for obtaining an accurate prediction. While previous QCT based FE studies on single vertebra reported strong to very strong correlations between experimentally determined and FE predicted vertebral strength [20, 21, 24-27, 29-31], the correlations we obtained were weak. The poorer strength prediction may be due to several differences between previous studies and the current models, in terms of (and among others) modelling approach, medical imaging data that was used for the models, and the loading configuration. Further research on, for example, disc and endplate mechanical properties, the role of the spinal ligaments and facet capsules, and the influence of loading conditions could aid in further optimization of the model.

Although validation is an essential step in modeling, one could debate to what extent FE models should be experimentally validated. In our FE model, validation could,

for example, aim for a correct prediction of the vertebrae that failed, strength, stiffness, applied axial displacement at failure, three-dimensional (3D) deformation of the entire specimen, or combinations of these. Since an *in vitro* environment is more controllable than an *in vivo* environment, validation is presumed to be easier in an experimental setting. However, it is also generally known that experiments are a simplification of reality. In our case, for example, the simulated metastases were rather different from lesions seen *in vivo* and the spinal orientation and subsequent (direction of) applied loads were simplified. When striving for an experimentally validated model, the model is optimized for functioning in a non-clinical setting, which not necessarily requires the same model characteristics as functioning in a clinical setting. Although the model should be experimentally validated based on the main outcome measure(s), as an alternative approach one could implement models in a more ‘premature’ state in clinical workflows. The model predictions should not yet interfere with treatment decision making in this stage, but comparing model predictions with actual clinical follow-up could provide valuable information on the model’s performance in a clinical setting and could identify areas requiring improvement. This way, the clinical setting, rather than the simplified experimental setting, directs model optimization after having experimentally validated the model based on the main outcome measure(s). This may prove to be a more efficient manner of model development than spending considerable amounts of resources to obtain a realistic simulation of experimental measurements. Hence, how to balance model development with experimental and clinical information is an interesting question for further discussions.

From an experiment-based FE model to a patient-based FE model

To demonstrate future clinical applicability of our FE model, we applied the workflow for generating FE models developed using *in vitro* experiments (**Chapter 6**) to a patient case from an ongoing prospective patient study (RACOST, ClinicalTrials.gov Identifier: NCT02407795) [32] (**Chapter 7**). The patients enrolled in this prospective study received radiotherapy to treat pain, thereby expected to have a low risk of vertebral fracture. The eventual aim of the FE models is to identify, before the start of radiotherapy, those patients who, after radiotherapy, will undergo an event. Such early identification might result in these patients receiving a surgical stabilizing procedure, thereby sustaining a more optimal quality of life. The transition from modeling cadaver experiments to *in vivo* strength assessment using FE models, however, identified a number of challenges.

For example, so far only simulated lytic metastatic lesions have been considered within both our experimental and FE model. As the elastic modulus of a lytic tumor is known to be orders of magnitude lower than the bone modulus (~30 kPa [33]), we dismissed the interaction of the tumor with the bone tissue. *In vivo*, however, metastatic bone lesions contain lytic or blastic metastatic tissue, or a combination of both. Whereas in lytic metastases bone resorption predominates, in blastic lesions mostly bone

deposition occurs. Therefore, the composition and mechanical behavior of metastatic bone tissue may be rather diverging and, consequently, may need adapted material models.

Sone et al. [34] found profound differences when comparing the 3D vertebral trabecular microarchitecture and degree of mineralization between blastic metastases and normal tissue. Trabecular osteoblastic tissue showed to have more, but equally thick trabeculae, resulting in an increased bone volume fraction. Also, metastatic tissue showed to be more irregularly shaped and isotropically arranged, as well as to have a higher degree of mineralization compared to healthy tissue. Unfortunately, the relationship between bone quality and bone strength was not studied. Hipp et al. [35] investigated whether, depending on the primary tumor type, density changes resulted in significant changes in mechanical properties by testing vertebral trabecular cubic bone specimens to failure in uniaxial compression. The Young's moduli of lytic and blastic specimens were lower than for normal specimens. In addition, the strength of lytic specimens was less than normal, while the strength of blastic specimens was not. Apparent density explained both the variations in both Young's modulus and strength. Thus, this data suggest that fracture risk predictors that utilize bone density to estimate stiffness or strength should adjust for the effects of metastases. However, Hipp et al. could not determine whether the relationships between density and mechanical properties changed by metastatic involvement. Both the studies by Sone et al. and Hipp et al. indicate that the mechanical features of tumor tissue could be significantly altered and could be an important factor in predicting fracture risk. In contrast, Kaneko et al. showed that metastatic disease (blastic, lytic and mixed lesions analyzed together) originating from femoral trabecular bone did not significantly alter the relationships between the mechanical properties (Young's modulus, strength) and bone density compared to healthy bone. This finding might be explained by the unequal distribution of the donors' gender and ages over the groups. Hence, this research area shows confusing and contradicting data and requires further research. Ideally, further studies should analyze the bone quality (e.g. 3D microarchitecture and degree of mineralization) of at least lytic, blastic, and normal vertebral bone specimens and, subsequently, load the specimens to failure while determining mechanical properties (e.g. Young's modulus, bone strength, and post-yield behavior). Finally, density measures should be established. Afterwards, the relationships between these measures of bone quality and bone density *versus* mechanical properties should be investigated within the same specimens. It should, however, be noted that the loading of specimens is complex and that only testing in axial compression does not capture bone behavior in full.

Furthermore, in the cadaver experiment we created artificial lesions by drilling cylindrical defects in the vertebral bodies and, subsequently, filled the resulting holes with a gel. Due to the simple and recognizable shape of the simulated lesion, the lesion could relatively easily be segmented and the corresponding elements could, subsequently, be deactivated. *In vivo*, however, these metastatic lesions present with

more irregular shapes and unclear borders. As a consequence, manually contouring the lesion in a CT image is more a complex and time- and labor-intensive process in an *in vivo* situation. Hence, an accurate and efficient automated delineation tool would benefit FE modeling. A promising method to do so is machine learning techniques. For example, convolutional neural networks, which are part of machine learning, consider segmentation tasks as classification problems and require a certain number of expert-segmented images to train classification models [36]. Based on those expert-segmented images, the computer learns itself to target abnormalities [37]. As such, the computer can be trained to automatically segment metastatic lesions. A difficulty in this remains, however, the need for a training set in which metastases are manually segmented in an accurate and reproducible manner.

Besides the difficulty of appropriate delineation of lesions, other typing of lesions seems equally difficult. The inter-observer agreement for indicating SINS component 'lesion type' based on CT images was fair ($\kappa = 0.299$, $p < 0.001$), suggesting that clinicians have difficulties with indicating whether a particular lesion is lytic, blastic or mixed (**Chapter 3**). In case future research shows that these tissue types show distinct mechanical behavior and require implementation in FE models, improved methods on lesion type characterization need to be developed. Possibly, machine learning algorithms could offer a solution for this as well.

Another challenge identified was related to the inclusion of patients. Since the goal of our study was to improve the assessment of (progressive) spinal instability and the percentage of patients sustaining a spinal fracture after radiotherapy is rather low (3 - 14% [5, 38, 39]), the total number of patients to be included in the study needs to be relatively high. Performing a multi-center rather than a single-center study aids in increasing the inclusion rate. Different institutes, however, will most likely use different scanners, whether or not from the same manufacturer, and will construct the CT images using different algorithms. Several studies have demonstrated that QCT-based FE predicted stiffness and/or bone strength can vary between models developed with different CT settings or scanners [40-42]. Carpenter et al. additionally showed that the inter-scanner differences remained, even when a bone mineral reference phantom was used for calibration of bone mineral concentration [40]. Therefore, these factors need to be considered when conducting multi-center studies using CT data for fracture risk prediction. In fact, these factors should also be considered when FE models from QCT scans for fracture prediction are generated in general. For example, these studies should at least state their acquisition protocols.

Radiological *versus* clinical spinal deformity

Our research mainly used bony deformities as outcome measures (**Chapters 4, 5, 6, and 7**). Although it is an essential first step, these bony deformities themselves are not the main issue when considering the care for patients with metastatic spinal bone disease. It

is their symptom burden, i.e. severe pain or impairing neurological problems, such as sphincter dysfunction or motor loss caused by compression of the spinal cord or root nerves, that steer the process of treatment decision making. Ideally, predictions should, therefore, not only be about whether or not a deformity occurs, but they should also be able to distinguish between deformities with and without occurring accompanying clinical symptoms (either pain or neurological problems). This implies that not only stiffness or strength should be considered using FE models, but that also e.g. (bony) deformation of the spinal canal and neural foramen need to be taken into account. Subsequently, this deformation needs to be related to the clinical complaints that patients suffer from. Switlyk et al. [43] analyzed the association between neurological function (Frankel score [44], a 5-point severity scale which classifies patients as complete neurological injury (grade A), preserved sensation only (grade B), preserved motor non-functional (grade C), preserved motor function (grade D), or no neurological deficit/complete recovery (grade E)) and MRI-based assessment of the degree of cord compression and spinal canal narrowing in patients with spinal bone metastases. They found that the percentage of patients with severe spinal canal narrowing increased with increasing Frankel grades. All patients with bone-only disease were ambulatory, while 62% of non-ambulatory patients had severe spinal canal narrowing. Conversely, 5% of patients with normal motor function had severe spinal narrowing. However, it is unclear whether reductions of the canal's area were, in this study, caused by bony deformation, and/or by direct tumor growth into the canal. As our current FE model only comprised bony tissue and IVDs, it could only predict canal narrowing due to bony deformation. However, there are currently no publications that correlate geometrical measures of the bony spinal canal and neural foramen to the neurological status in patients with spinal bone metastases. Further research on this topic is required.

In addition, radiological imaging of patients with spinal metastases may also show growth of metastatic tissue from the vertebrae into the spinal canal and foramina. Neurological problems can, consequently, also be caused by tumor growth rather than bony deformation. As stated above, the FE model developed in this thesis does not consider tumor growth. However, currently mathematical models predicting the progress of tumor growth and metastasis and devising optimal treatment strategies, such as for chemo- and or radiotherapy, are being developed [45-47]. Although these models on tumor growth are in its infancy, future incorporation of such models in FE models predicting failure behavior might be of added value for the prediction of impending neurological symptoms.

Radiotherapy to stabilize metastatically affected bones

Although the clinical experience of many physicians is that after radiotherapy recalcification occurs, especially after higher doses of radiotherapy, current literature does not contain sufficient evidence to support these observations (**Chapter 8**). In **Chapter 8**

we concluded that, although associated with several methodological, practical, and ethical challenges, prospective trials are needed to assess the effect of radiotherapy, with and without adjunct bisphosphonates or receptor activator of nuclear factor kappa- β ligand (RANKL) inhibitors, on bone quality and bone strength. The Utrecht University Medical Center's Prospective Evaluation of Interventional Studies on Bone Metastases (PRESENT) cohort (ClinicalTrials.gov Identifier: NCT02356497), which is set up according to the 'cohort multiple Randomized Controlled Trial' design, is an example of a prospective cohort suitable for evaluating the effects of radiotherapy. The benefits of a prospective design with respect to data collection that hold for evaluating the predictive power of the SINS also count for future studies on the stabilizing effect of radiotherapy. Using a prospective study, one can, for example, systematically investigate potential short- and long-term effects by obtaining follow-up scans on a regular basis, and standardize the scan settings to, in case of CT, account for scan setting-induced differences in Hounsfield Units. Of course, protocols as these go with practical as well as moral issues regarding follow-up in a population of patients with a limited life expectancy and might, therefore, be difficult to perform. Preferably, future studies determine outcome measures related to bone quality as well as related to fracture risk within the same subject. This way, correlations between bone quality and bone strength could be calculated on a subject-to-subject basis, which might provide insight in the mechanisms through which radiotherapy affects bone tissue.

Alternative applications of models on predictions of spinal instability

Although further improvements are essential, the research performed within this project formed a basis for an FE modelling workflow for assessing vertebral bone strength. The experimental and FE models developed in this work have alternative (future) applications.

The current FE model uses a pre-treatment CT scan as input information, thereby disregarding any possible temporal changes to bone quality. However, it is well established that anticancer treatments such as chemotherapy and hormone therapy, may induce bone loss [48, 49]. Conversely, bisphosphonates and RANKL inhibitors (denosumab) have shown to positively affect bone quality over time [50-53]. In addition, disease progression often results in a decreased bone quality. Currently, such treatment effects can be evaluated in terms of bone mineral density (BMD), generally determined using imaging techniques such as dual-energy X-ray absorptiometry (DEXA) or CT. Finite element models could be of added value by further translating these findings to patient-specific bone strength. For example, Kopperdahl et al. showed that FE derived bone strength was a stronger predictor for spinal fractures in osteoporotic patients than BMD measures [54]. Therefore, these results illustrate that FE analyses could be of added value in fracture risk assessment, and, subsequently, potentially in treatment evaluations. In the same vein, **Chapter 8** concluded that there was no sufficient evidence

that radiotherapy, whether or not with bisphosphonates or RANKL inhibitors as adjunct therapy, had a positive effect on bone quality and fracture risk. However, the effect of radiotherapy on vertebral strength has not yet been assessed using FE models. Possibly, the use of FE models could provide further insight in radiotherapy effects, as FE models can capture the effects of local density changes on structural bone strength.

By repeatedly acquiring CT scans during and after treatment and, subsequently, re-running FE models, one can take treatment- and/or tumor-induced changes in bone quality into account when predicting bone strength. Based on these repetitive predictions, treatment decisions could be revised or advice could be given on daily activities that can and/or cannot safely be performed. In this way, the prediction of the FE models can be used to further personalize the patient's treatment.

Next to evaluating systemic treatments, research on the effect of local techniques on spinal instability could benefit from the experimental and FE models developed within this thesis. For example, biomechanical studies on vertebroplasty have largely focused on the effects of cement augmentation in single vertebrae or vertebral bodies. In contrast, multi-level spine models, which provide a more realistic anatomical configuration with load bearing discs and vertebral bodies above and below the vertebral body of interest, are limited and are more heterogeneous in terms of methodology, parameters studied, and results [55]. Thus, more studies using multi-level spine models are required, to which the currently developed models could be of benefit.

Furthermore, the application of the experimental and FE models are not limited to metastatic disease. Osteoporosis, for example, is also characterized by reductions in bone quality, leading to an increased susceptibility to fracture. Bones that commonly break in osteoporotic patients include the vertebrae, the bones of the forearm, and the hip [56]. The FE model developed within this thesis could also aid in fracture risk prediction in osteoporosis in order to serve as a useful clinical tool when deciding on treatment, e.g. bisphosphonates or spinal surgery. Currently, these techniques are being commercialized. For example, the FDA-cleared VirtuOst software (O.N. Diagnostics, Berkeley, California, United States) is used to identify osteoporosis, assess fracture risk, and monitor treatments based on CT scans [57]. However, these calculations are based on single vertebrae. The 3-unit spinal segmental model developed in the current work could aid in making the predictions more anatomically correct.

Concluding remarks

The goal of this work was to improve the assessment of spinal (in)stability in patients with cancer suffering from spinal bone metastases and, as a consequence, the multidisciplinary care for these patients. It cannot be emphasized enough that treatment decision making in clinical practice is a rather complex and in time varying process, which does not solely depend on estimating spinal instability. Factors such as the patient's estimated life expectancy, clinical performance, other symptoms and

complaints on the physical, psychosocial, and spiritual domains that are present in the palliative phase of disease, together with the patient's values and wishes, are of utmost importance and need to be taken into account.

In this thesis, the assessment of spinal instability has been approached from several different points of view. This work shows that estimating spinal instability plays an increasingly important role in proactive rather than reactive treatment decision making in patients with cancer and spinal bone metastases, but current clinical practice omits validated tools for assessing spinal instability. The predictive capacity of the recently introduced SINS to discriminate between lesions at risk and not at risk of progressive debilitating instability was shown to remain uncertain, but the SINS has its value in increasing the awareness of instability among the involved multidisciplinary clinicians taking care of this complex patient group. As a more biomechanical counterpart, in this thesis an FE model of 3-segment spinal units to predict failure behavior was developed and partly validated against experiments. Although being a promising tool, the current FE model requires substantial improvements before it can be referred to as experimentally validated, be demonstrated to outperform clinicians, and be tested what the models' predictive capacity *in vivo* is (clinical validation). In addition, it was demonstrated that there was no sufficient evidence in the current literature that radiotherapy, whether or not with bisphosphonates or RANKL inhibitors as adjunct to radiotherapy, had a positive effect on bone quality and fracture risk in patients with metastatic bone disease.

The work described in this thesis has laid a basis for improved methods for assessing spinal instability. In addition, it has contributed to the identification of difficulties towards development and implementation of these improved methods. Improved assessment of spinal instability will aid patients and their treating physicians to make a proactive treatment plan, in which decisions, e.g. to irradiate for pain reduction, perform surgical interventions to preserve or restore spinal stability, or a combination of these, are considered more adequately and with an eye on future complications. Eventually, improved treatment decision making will result in more optimal and individualized care for patients with cancer and spinal bone metastases, and has the potential to prevent progressive spinal instability and neurological problems. This can lead to maintenance of function and improvement, or at least stabilization, of quality of life in patients with cancer and spinal bone metastases.

References

1. Fisher CG, DiPaola CP, Ryken TC, Bilsky MH, Shaffrey CI, Berven SH, Harrop JS, Fehlings MG, Boriani S, Chou D, Schmidt MH, Polly DW, Biagini R, Burch S, Dekutoski MB, Ganju A, Gerszten PC, Gokaslan ZL, Groff MW, Liebsch NJ, Mendel E, Okuno SH, Patel S, Rhines LD, Rose PS, Sciubba DM, Sundaresan N, Tomita K, Varga PP, Vialle LR, Vrionis FD, Yamada Y, Fourny DR. A novel classification system for spinal instability in neoplastic disease: an evidence-based approach and expert consensus from the Spine Oncology Study Group. *Spine (Phila Pa 1976)* 2010;35(22):E1221-1229.
2. Cunha MV, Al-Omair A, Atenafu EG, Masucci GL, Letourneau D, Korol R, Yu E, Howard P, Lochray F, da Costa LB, Fehlings MG, Sahgal A. Vertebral compression fracture (VCF) after spine stereotactic body radiation therapy (SBRT): analysis of predictive factors. *Int J Radiat Oncol Biol Phys* 2012;84(3):e343-349.
3. Germano IM, Carai A, Pawha P, Blackburg S, Lo YC, Green S. Clinical outcome of vertebral compression fracture after single fraction spine radiosurgery for spinal metastases. *Clin Exp Metastasis* 2016;33(2):143-149.
4. Lee SH, Tatsui CE, Ghia AJ, Amini B, Li J, Zavarella SM, Tannir NM, Brown PD, Rhines LD. Can the spinal instability neoplastic score prior to spinal radiosurgery predict compression fractures following stereotactic spinal radiosurgery for metastatic spinal tumor?: a post hoc analysis of prospective phase II single-institution trials. *J Neurooncol* 2016;126(3):509-517.
5. Sahgal A, Atenafu EG, Chao S, Al-Omair A, Boehling N, Balagamwala EH, Cunha M, Thibault I, Angelov L, Brown P, Suh J, Rhines LD, Fehlings MG, Chang E. Vertebral compression fracture after spine stereotactic body radiotherapy: a multi-institutional analysis with a focus on radiation dose and the spinal instability neoplastic score. *J Clin Oncol* 2013;31(27):3426-3431.
6. Lam TC, Uno H, Krishnan M, Lutz S, Groff M, Cheney M, Balboni T. Adverse Outcomes After Palliative Radiation Therapy for Uncomplicated Spine Metastases: Role of Spinal Instability and Single-Fraction Radiation Therapy. *Int J Radiat Oncol Biol Phys* 2015;93(2):373-381.
7. Aiba H, Kimura T, Yamagami T, Watanabe N, Sakurai H, Kimura H, Shimozaki S, Yamada S, Otsuka T. Prediction of skeletal-related events in patients with non-small cell lung cancer. *Support Care Cancer* 2016;24(8):3361-3367.
8. Versteeg AL, van der Velden JM, Verkooyen HM, van Vulpen M, Oner FC, Fisher CG, Verlaan JJ. The Effect of Introducing the Spinal Instability Neoplastic Score in Routine Clinical Practice for Patients With Spinal Metastases. *Oncologist* 2016;21(1):95-101.
9. Dimar JR, 2nd, Voor MJ, Zhang YM, Glassman SD. A human cadaver model for determination of pathologic fracture threshold resulting from tumorous destruction of the vertebral body. *Spine (Phila Pa 1976)* 1998;23(11):1209-1214.
10. Ebihara H, Ito M, Abumi K, Taneichi H, Kotani Y, Minami A, Kaneda K. A biomechanical analysis of metastatic vertebral collapse of the thoracic spine: a sheep model study. *Spine (Phila Pa 1976)* 2004;29(9):994-999.
11. Tschirhart CE, Finkelstein JA, Whyne CM. Metastatic burst fracture risk assessment based on complex loading of the thoracic spine. *Ann Biomed Eng* 2006;34(3):494-505.
12. Tschirhart CE, Finkelstein JA, Whyne CM. Biomechanics of vertebral level, geometry, and transcortical tumors in the metastatic spine. *J Biomech* 2007;40(1):46-54.
13. Tschirhart CE, Nagpurkar A, Whyne CM. Effects of tumor location, shape and surface serration on burst fracture risk in the metastatic spine. *J Biomech* 2004;37(5):653-660.
14. Whealan KM, Kwak SD, Tedrow JR, Inoue K, Snyder BD. Noninvasive imaging predicts failure load of the spine with simulated osteolytic defects. *J Bone Joint Surg Am* 2000;82(9):1240-1251.
15. Whyne CM, Hu SS, Klisch S, Lotz JC. Effect of the pedicle and posterior arch on vertebral body strength predictions in finite element modeling. *Spine (Phila Pa 1976)* 1998;23(8):899-907.
16. Whyne CM, Hu SS, Lotz JC. Burst fracture in the metastatically involved spine: development, validation, and parametric analysis of a three-dimensional poroelastic finite-element model. *Spine (Phila Pa 1976)* 2003;28(7):652-660.
17. Windhagen HJ, Hipp JA, Silva MJ, Lipson SJ, Hayes WC. Predicting failure of thoracic vertebrae with simulated and actual metastatic defects. *Clin Orthop Relat Res* 1997(344):313-319.

18. Derikx LC, van Aken JB, Janssen D, Snyers A, van der Linden YM, Verdonshot N, Tanck E. The assessment of the risk of fracture in femora with metastatic lesions: comparing case-specific finite element analyses with predictions by clinical experts. *J Bone Joint Surg Br* 2012;94(8):1135-1142.
19. Eggermont F, Derikx LC, Verdonshot N, Van der Geest ICM, De Jong MAA, Snyers A, Van der Linden YM, Tanck E. Can patient-specific finite element models better predict fractures in metastatic bone disease than experienced clinicians? Towards introducing computational modelling into daily clinical practice. *Bone and Joint Research* submitted.
20. Chevalier Y, Charlebois M, Pahr D, Varga P, Heini P, Schneider E, Zysset P. A patient-specific finite element methodology to predict damage accumulation in vertebral bodies under axial compression, sagittal flexion and combined loads. *Comput Methods Biomech Biomed Engin* 2008;11(5):477-487.
21. Chevalier Y, Pahr D, Charlebois M, Heini P, Schneider E, Zysset P. Cement distribution, volume, and compliance in vertebroplasty: some answers from an anatomy-based nonlinear finite element study. *Spine (Phila Pa 1976)* 2008;33(16):1722-1730.
22. Chevalier Y, Pahr D, Zysset PK. The role of cortical shell and trabecular fabric in finite element analysis of the human vertebral body. *J Biomech Eng* 2009;131(11):111003.
23. Matsuura Y, Giambini H, Ogawa Y, Fang Z, Thoreson AR, Yaszemski MJ, Lu L, An KN. Specimen-specific nonlinear finite element modeling to predict vertebrae fracture loads after vertebroplasty. *Spine (Phila Pa 1976)* 2014;39(22):E1291-1296.
24. Pahr DH, Schwiedrzik J, Dall'Ara E, Zysset PK. Clinical versus pre-clinical FE models for vertebral body strength predictions. *J Mech Behav Biomed Mater* 2014;33:76-83.
25. Liebschner MA, Kopperdahl DL, Rosenberg WS, Keaveny TM. Finite element modeling of the human thoracolumbar spine. *Spine (Phila Pa 1976)* 2003;28(6):559-565.
26. Buckley JM, Loo K, Motherway J. Comparison of quantitative computed tomography-based measures in predicting vertebral compressive strength. *Bone* 2007;40(3):767-774.
27. Crawford RP, Cann CE, Keaveny TM. Finite element models predict in vitro vertebral body compressive strength better than quantitative computed tomography. *Bone* 2003;33(4):744-750.
28. Dall'Ara E, Schmidt R, Pahr D, Varga P, Chevalier Y, Patsch J, Kainberger F, Zysset P. A nonlinear finite element model validation study based on a novel experimental technique for inducing anterior wedge-shape fractures in human vertebral bodies in vitro. *J Biomech* 2010;43(12):2374-2380.
29. Imai K. Analysis of vertebral bone strength, fracture pattern, and fracture location: a validation study using a computed tomography-based nonlinear finite element analysis. *Aging Dis* 2015;6(3):180-187.
30. Imai K, Ohnishi I, Bessho M, Nakamura K. Nonlinear finite element model predicts vertebral bone strength and fracture site. *Spine (Phila Pa 1976)* 2006;31(16):1789-1794.
31. Mirzaei M, Zeinali A, Razmjoo A, Nazemi M. On prediction of the strength levels and failure patterns of human vertebrae using quantitative computed tomography (QCT)-based finite element method. *J Biomech* 2009;42(11):1584-1591.
32. Braam P, Lambin P, Bussink J. Stereotactic versus conventional radiotherapy for pain reduction and quality of life in spinal metastases: study protocol for a randomized controlled trial. *Trials* 2016;17:61.
33. Whyne CM, Hu SS, Lotz JC. Parametric finite element analysis of vertebral bodies affected by tumors. *J Biomech* 2001;34(10):1317-1324.
34. Sone T, Tamada T, Jo Y, Miyoshi H, Fukunaga M. Analysis of three-dimensional microarchitecture and degree of mineralization in bone metastases from prostate cancer using synchrotron microcomputed tomography. *Bone* 2004;35(2):432-438.
35. Hipp JA, Rosenberg AE, Hayes WC. Mechanical properties of trabecular bone within and adjacent to osseous metastases. *J Bone Miner Res* 1992;7(10):1165-1171.
36. Liu F, Zhou Z, Jang H, Samsonov A, Zhao G, Kijowski R. Deep convolutional neural network and 3D deformable approach for tissue segmentation in musculoskeletal magnetic resonance imaging. *Magn Reson Med* 2017.
37. Moeskops P, Viergever MA, Mendrik AM, de Vries LS, Benders MJ, Išgum I. Automatic Segmentation of MR Brain Images With a Convolutional Neural Network. *IEEE Trans Med Imaging* 2016;35(5):1252-1261.

38. Sze WM, Shelley M, Held I, Mason M. Palliation of metastatic bone pain: single fraction versus multifraction radiotherapy - a systematic review of the randomised trials. *Cochrane Database Syst Rev* 2004(2):CD004721.
39. Chow E, Harris K, Fan G, Tsao M, Sze WM. Palliative radiotherapy trials for bone metastases: a systematic review. *J Clin Oncol* 2007;25(11):1423-1436.
40. Carpenter RD, Saeed I, Bonaretti S, Schreck C, Keyak JH, Streeper T, Harris TB, Lang TF. Inter-scanner differences in in vivo QCT measurements of the density and strength of the proximal femur remain after correction with anthropomorphic standardization phantoms. *Med Eng Phys* 2014;36(10):1225-1232.
41. Giambini H, Dragomir-Daescu D, Nassr A, Yaszemski MJ, Zhao C. Quantitative Computed Tomography Protocols Affect Material Mapping and Quantitative Computed Tomography-Based Finite-Element Analysis Predicted Stiffness. *J Biomech Eng* 2016;138(9).
42. Lu Y, Engelke K, Puschel K, Morlock MM, Huber G. Influence of 3D QCT scan protocol on the QCT-based finite element models of human vertebral cancellous bone. *Med Eng Phys* 2014;36(8):1069-1073.
43. Switlyk MD, Hole KH, Skjeldal S, Hald JK, Knutstad K, Seierstad T, Zaikova O. MRI and neurological findings in patients with spinal metastases. *Acta radiol* 2012;53(10):1164-1172.
44. Frankel HL, Hancock DO, Hyslop G, Melzak J, Michaelis LS, Ungar GH, Vernon JD, Walsh JJ. The value of postural reduction in the initial management of closed injuries of the spine with paraplegia and tetraplegia. I. Paraplegia 1969;7(3):179-192.
45. Bethge A, Schumacher U, Wedemann G. Simulation of metastatic progression using a computer model including chemotherapy and radiation therapy. *J Biomed Inform* 2015;57:74-87.
46. Razavi MJ, Reeves M, Wang X. Mechanical role of a growing solid tumor on cortical folding. *Comput Methods Biomech Biomed Engin* 2017;20(11):1212-1222.
47. Zacharakis EI, Hogeia CS, Shen D, Biros G, Davatzikos C. Non-diffeomorphic registration of brain tumor images by simulating tissue loss and tumor growth. *Neuroimage* 2009;46(3):762-774.
48. Nguyen PL, Alibhai SM, Basaria S, D'Amico AV, Kantoff PW, Keating NL, Penson DF, Rosario DJ, Tombal B, Smith MR. Adverse effects of androgen deprivation therapy and strategies to mitigate them. *Eur Urol* 2015;67(5):825-836.
49. Saad F, Adachi JD, Brown JP, Canning LA, Gelmon KA, Josse RG, Pritchard KI. Cancer treatment-induced bone loss in breast and prostate cancer. *J Clin Oncol* 2008;26(33):5465-5476.
50. LeVasseur N, Clemons N, Hutton B, Shorr R, Jacobs C. Bone-targeted therapy use in patients with bone metastases from lung cancer: A systematic review of randomized controlled trials. *Cancer Treat Rev* 2016;50:183-193.
51. Lopez-Olivo MA, Shah NA, Pratt G, Risser JM, Symanski E, Suarez-Almazor ME. Bisphosphonates in the treatment of patients with lung cancer and metastatic bone disease: a systematic review and meta-analysis. *Support Care Cancer* 2012;20(11):2985-2998.
52. Yuen KK, Shelley M, Sze WM, Wilt T, Mason MD. Bisphosphonates for advanced prostate cancer. *Cochrane Database Syst Rev* 2006(4):CD006250.
53. Boyle WJ, Simonet WS, Lacey DL. Osteoclast differentiation and activation. *Nat New Biol* 2003;423(6937):337-342.
54. Kopperdahl DL, Aspelund T, Hoffmann PF, Sigurdsson S, Siggeirsdottir K, Harris TB, Gudnason V, Keaveny TM. Assessment of incident spine and hip fractures in women and men using finite element analysis of CT scans. *J Bone Miner Res* 2014;29(3):570-580.
55. Tan E, Wang T, Pelletier MH, Walsh WR. Effects of cement augmentation on the mechanical stability of multilevel spine after vertebral compression fracture. *J Spine Surg* 2016;2(2):111-121.
56. Johnell O, Kanis JA. An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. *Osteoporos Int* 2006;17(12):1726-1733.
57. O.N. diagnostics. VirtuOst Bone Strength Assessment. Last accessed 2017. Available from: <https://ondiagnostics.com/>.



10

Summary

Increasing cancer incidence rates together with prolonged survival will result in more cancer patients being confronted with the clinical consequences of spinal bone metastases. Estimating current or future spinal instability or stability plays an important role in treatment decisions on whether to use non-invasive local therapies such as radiotherapy or to perform stabilizing surgical interventions, or combinations of these. However, due to the absence of validated guidelines or an established predefined set of risk factors, the assessment of spinal stability in metastatic bone disease is challenging and is mostly done by relying on the clinical experience of involved physicians. The goal of this work was to improve the assessment of spinal (in)stability in patients suffering from metastatic spinal bone disease and, as a consequence, the multidisciplinary care for these patients. In this thesis, this topic has been approached from several different points of view. The current chapter summarizes the key findings of this thesis.

Chapter 2 described the main results of the evidence-based approach to develop the Dutch national guideline on metastases of solid tumors and hematological malignancies localized within the spine. Goals were to create a comprehensive guideline focusing on the following four important principles: (1) The patient's perspective is leading (patient participation); (2) Proactive management is directed at preventing complications; (3) Clear treatment selection criteria are defined; and (4) Organization, communication, and coordination of care is optimized. The guideline was drafted by a national multidisciplinary panel consisting of clinicians, a nurse, a patient advocate, an epidemiologist, and a methodologist. Following a bottleneck analysis, fourteen clinical questions were addressed using either an evidence- or consensus-based approach. The resulting guideline explicitly pursues proactive, multidisciplinary patient care and gives recommendations about diagnostics, treatment modalities, patient selection, follow-up, organization of care, and palliative care. In Chapter 2 practical considerations regarding the guideline's implementation were also discussed.

The recently developed Spinal Instability Neoplastic Score (SINS) uses both patient related factors and radiological parameters determined from computed tomography (CT) image data to register spinal instability due to metastatic disease. **Chapter 3** evaluated the predictive value of the SINS. This retrospective cohort study included 110 patients treated with radiotherapy for spinal bone metastases in the Leiden University Medical Center. Using pre-treatment CT scans the affected vertebrae were scored according to the SINS criteria. The end points of the study were considered adverse events after radiotherapy and consisted of (1) the development of a new pathological fracture, (2) progression of an existing pathological fracture, and (3) deterioration of alignment requiring surgical stabilization of the irradiated spinal segments. The occurrence of an adverse event was determined using patients' medical charts and/or follow-up imaging, up to 12 months after initial radiotherapy. Using a competing risk analysis the effect of the SINS on the cumulative incidence of the occurrence of an adverse event was estimated. Sixteen patients (15%) experienced an adverse event during follow-up. The competing risk analysis showed that the final SINS classification

was not significantly associated with the cumulative incidence of an adverse event within the studied population. Therefore, we concluded that the clinical applicability of the SINS as a tool to assess impending spinal instability seemed limited.

Another approach for assessing spinal instability is the use of case-specific finite element (FE) models. This thesis aimed to develop and optimize a workflow for generating case-specific FE models, to validate it against mechanical experiments, and to show its clinical application in actual patient data (**Chapters 4-7**).

In **Chapter 4** an experimental setup and protocol able to induce targeted failure in 3-segment spinal units was developed. Three-segment spinal units comprised three consecutive vertebrae and two intervertebral discs (IVDs). *In vitro* mechanical experiments were performed in which cadaveric 3-segment spinal units with and without simulated metastatic lesions were destructively tested in axial compression. To verify whether failure only occurred in the middle vertebra and to capture the three-dimensional (3D) deformation of the entire specimen, CT scans of the specimens fully fixated in polymethylmethacrylate (PMMA), thereby preserving the post-failure state, were acquired and evaluated. Initially, the commonly used 'clear drop in force failure criterion' (>10 - 15% drop in peak force) was adopted. However, it was shown that this failure criterion did not sufficiently result in targeted failure of the middle vertebrae. Consequently, a new failure criterion was introduced, being a minimum applied displacement of 5 mm. This new failure criterion increased the probability of inducing fractures in the target vertebrae. Vertebral bone strength was determined for the experiments in which only the middle vertebrae showed signs of failure.

In order to assess whether newly developed scoring systems, such as the SINS or FE models, improve upon clinical practice, current assessment skills of clinicians on fracture risk prediction should be determined. Therefore, in **Chapter 5**, we studied how accurate experienced clinicians were at predicting the strength of vertebrae with simulated metastatic lesions and determined what imaging modality - magnetic resonance (MR) images, CT scans, and/or dual energy X-ray absorptiometry (DEXA) scans - they needed to best predict vertebral strength. To that end, four experienced clinicians were asked to rank the experimentally tested 3-segment spinal units from Chapter 4 on failure load using different imaging modalities (MRI, CT, and/or DEXA). Not only did we observe large variations between clinicians ($\tau = 0.111$ ($p > 0.05$) - 0.778 ($p < 0.01$)), we also saw that clinicians performed inconsistently in repeated ranking tasks, even though they had the same imaging information at their disposal. This might not only indicate that clinicians use their own experience and rely on different determinants to assess vertebral strength, but also that they use varying strategies over time. These observations likely introduce variation in patient treatment in clinical reality. In addition, ranking of the vertebrae showed large variations in relation to imaging modality. Therefore, the present study did not provide conclusive evidence about the optimal imaging modality for prediction of bone strength. We concluded that the results found underline the urge

for a more objective protocol or method to assess vertebral strength and, hence, to improve clinical care of patients with spinal bone metastases.

In **Chapter 6**, we aimed to develop a case-specific non-linear FE model of 3-segment spinal units able to predict failure behavior in terms of (a) the vertebra predicted to fail; (b) the deformation of the entire specimen; (c) stiffness; and (d) load to failure. Furthermore, we studied the effects of different relationships between bone density and mechanical properties (material models) on the prediction of failure behavior. The specimens tested as described in Chapter 4 were simulated using case-specific non-linear FE models. Bone material properties were assigned using four commonly used material models. In 11 of the 12 specimens our FE model was able to correctly indicate which vertebra failed during the experiments. However, predictions of 3D deformations of the entire specimens were less promising, particularly in cases of endplate failure. Whereas stiffness of the whole construct could be strongly predicted ($R^2 = 0.637 - 0.688$, $p < 0.01$), we obtained weak correlations between FE predicted and experimentally determined load to failure ($R^2 = 0.219 - 0.247$, $p > 0.05$). Additionally, we found that the correlation between predicted and experimental fracture loads did not strongly depend on the material model implemented, but the stiffness predictions did. In conclusion, this work showed that, in its current state, our FE models may be used to identify the weakest vertebra, but that substantial improvements are required in order to quantify *in vivo* failure loads.

Nevertheless, in **Chapter 7** we demonstrated the workflow for generating FE models of 3-segment spinal units, as developed in Chapter 6, to a first real patient case. This exploratory study aimed to demonstrate whether modeling physiological load cases instead of a simple loading regime can significantly affect failure predictions. The patient concerned had a lytic metastatic lesion in the fourth lumbar (L4) vertebra and sustained a pathological fracture 11 months after radiotherapy. An FE model of the patient's L3-L5 spine was generated using the workflow described in Chapter 6 and, subsequently, an experimental loading condition (axial compression) was applied. Furthermore, we applied more physiological loading conditions to the L3-L5 spinal unit. The musculoskeletal Twente Spine Model (MSM) was used to predict compression and shear forces at the intervertebral joints during the following movements: 45° flexion, 90° flexion, 15° extension, 15° right lateral bending, and 15° left lateral bending. These joint forces were subsequently applied to the FE model. We found that none of the physiological movements but flexion induced plasticity. In addition, the joint force in 45° flexion was considerably lower than the force needed to induce the same amount of plasticity under axial compression. This might indicate that the vertebra under study was more prone to failure under flexion than under pure compression. This study demonstrated a first attempt to combine musculoskeletal and FE modeling in a real patient case and further explored the implementation of the workflow developed in Chapter 6 in clinical practice. Modeling physiological load cases instead of a simple loading regime affected the failure predictions, indicating that for *in vivo* fracture

prediction physiological load cases should be considered. Nevertheless, substantial improvements regarding the FE model, MSM, as well as combining MSMs and FE models are required in order to be able to predict the risk of failure under physiological loads. Therefore, this study should be seen as a demonstration for future applications.

Next, we investigated whether non-invasive therapies, as opposed to immediately stabilizing though invasive surgery, have a bone stabilizing effect. **Chapter 8** described a systematic literature study in which the effects of (1) radiotherapy; (2) radiotherapy combined with bisphosphonates; and (3) radiotherapy combined with receptor activator of nuclear factor kappa- β ligand (RANKL) inhibitors on bone quality and bone strength in bone metastases originating from solid tumors were assessed. Pubmed, EMBASE and the Cochrane Library were searched using search terms for bone metastases, radiotherapy, bisphosphonates, RANKL inhibitors, bone mineral density, bone quality and bone strength. Original studies using radiotherapy, BPs, and RANKL inhibitors of any type and dosage, in both patients and animals, were allowed. In this study we focused on biomechanical outcome measures: re-calcification, bone density, bone micro-architecture, bone strength, and pathological fractures. Of the 3273 retrieved records, 39 studies (3 on animals, 36 on humans) were included in this systematic review. Although radiotherapy has proven to be an effective treatment for pain reduction in bone metastases and in clinical practice there are numerous cases in which re-calcification is observed through follow-up diagnostic imaging, based on this systematic review there was no sufficient published evidence for an additional positive effect of radiotherapy on bone quality and fracture risk. In addition, animal studies showed that adding bisphosphonates to radiotherapy restored bone quality and strength to that of healthy bone, whereas this has not yet been proven in patients. Finally, there were no studies addressing the adjunct effect of RANKL inhibitors to radiotherapy. We concluded that, although associated with several methodological, practical, and ethical challenges, randomized trials to assess the influence of radiotherapy on bone re-calcification and subsequent bone strength are needed.

In the discussion presented in **Chapter 9** we reflected on the work described in this thesis and on future challenges to further improve the assessment of spinal instability.



11

Samenvatting

De stijgende incidentie van kanker en langere levensduur van patiënten met kanker zorgen ervoor dat deze patiënten in toenemende mate geconfronteerd zullen gaan worden met wervelmetastasen. Wervelmetastasen kunnen verschillende klachten veroorzaken, waaronder pijn, het inzakken van de wervel en neurologische problemen. Wervelmetastasen kunnen op verschillende manieren behandeld worden. Men kan bijvoorbeeld inzetten op een minimaal belastende behandeling zoals radiotherapie, op het chirurgisch stabiliseren van de aangedane wervel(s) of op combinaties hiervan. Bij de behandelkeuze speelt het inschatten van (verwachte) wervelstabiliteit of -instabiliteit een belangrijke rol. Om wervelinstabiliteit te bepalen zijn correcte voorspellers nodig. In de huidige klinische praktijk zijn deze echter niet nauwkeurig genoeg. Het is voor artsen momenteel dan ook erg lastig om een inschatting te maken van de mate van wervelinstabiliteit. Het werk beschreven in dit proefschrift beoogde het vaststellen van wervel(in)stabiliteit bij patiënten met wervelmetastasen te verbeteren en, mede daardoor, de multidisciplinaire zorg omtrent deze patiëntengroep te verbeteren. In dit proefschrift werd dit onderwerp vanuit verschillende invalshoeken belicht. Dit hoofdstuk vat de belangrijkste bevindingen van dit proefschrift samen.

Hoofdstuk 2 beschreef de belangrijkste resultaten van de ‘evidence-based’ Nederlandse richtlijn over wervelmetastasen afkomstig van solide tumoren en hematologische maligniteiten. Deze richtlijn gaat uit van vier belangrijke principes: (1) de patiënt staat centraal; (2) een proactief beleid gericht op het voorkomen van complicaties; (3) het stellen van duidelijke selectiecriteria voor behandelingen en (4) verbeterde organisatie, communicatie en coördinatie van zorg. De richtlijn is opgesteld door een landelijke, multidisciplinaire werkgroep bestaande uit artsen, een verpleegkundige, een patiëntvertegenwoordiger, een epidemioloog en een methodoloog. Na het uitvoeren van een knelpuntenanalyse zijn er 14 klinische vragen opgesteld die vervolgens ‘evidence- of consensus-based’ beantwoord zijn. De uiteindelijke richtlijn streeft nadrukkelijk proactieve en multidisciplinaire zorg na en geeft aanbevelingen op het gebied van diagnostiek, behandelingsmogelijkheden, patiëntselectie, nabehandeling, organisatie van zorg en palliatieve zorg. In **Hoofdstuk 2** worden tevens praktische zaken omtrent het implementeren van de richtlijn in de klinische praktijk besproken.

De recent ontwikkelde ‘Spinal Instability Neoplastic Score’ (SINS) bepaalt de mate van wervelinstabiliteit als gevolg van metastasen aan de hand van radiologische en patiëntgerelateerde karakteristieken. De radiologische kenmerken worden bepaald op basis van computertomografie (CT) scans. In **Hoofdstuk 3** werd de voorspellende waarde van de SINS door middel van een retrospectieve cohort studie geëvalueerd. Het cohort bestond uit 110 patiënten met wervelmetastasen die in het Leids Universitair Medisch Centrum met radiotherapie behandeld zijn. Van deze patiënten is de SINS score bepaald aan de hand van CT scans die voorafgaand aan de behandeling werden gemaakt. We volgden deze patiënten tot en met een jaar na de behandeling en stelden vast of er in deze periode een van de volgende complicaties (adverse events) optrad: (1) een nieuwe

pathologische fractuur; (2) progressie van een bestaande pathologische fractuur en (3) noodzaak tot chirurgische stabilisatie van de bestraalde wervels als gevolg van verdere standsverandering van de wervels. Patiëntendossiers en beschikbare beeldvorming werden gebruikt om het al dan niet optreden van deze adverse events vast te stellen. Zestien patiënten (15%) bleken een adverse event te hebben doorgemaakt. Uit een competing risk analyse bleek dat, in deze studiegroep, de SINS score niet geassocieerd was met de cumulatieve incidentie van een adverse event. We concludeerden daarom dat de klinische toepasbaarheid van de SINS in zijn huidige vorm als een methode voor het vaststellen van (verwachte) wervelinstabiliteit beperkt was.

Een alternatieve aanpak voor het vaststellen van wervelinstabiliteit betreft het gebruik van subject-specifieke eindige elementen (EE) modellen. Dit proefschrift had daarom als doel om een subject-specifiek EE model te ontwikkelen, dit model te valideren aan de hand van mechanische experimenten met donorbotten en de klinische toepassing ervan in een patiënt met wervelmetastasen te demonstreren (**Hoofdstukken 4-7**).

In **Hoofdstuk 4** ontwikkelden we een experimentele setup en bijbehorend protocol om een breuk te laten ontstaan in de middelste wervel van proefstukken die bestonden uit drie opeenvolgende wervels, inclusief twee tussenwervelschijven. In deze proefstukken werden gaten geboord die leken op osteolytische uitzaaiingen in de wervels van patiënten met kanker. Deze botten werden in een trekbank onder compressie belast totdat ze braken. Om te kunnen vaststellen of daadwerkelijk enkel de middelste wervel gebroken was, werden de proefstukken na het breken volledig gefixeerd in botcement. Vervolgens maakten en analyseerden we CT scans van deze gefixeerde proefstukken. Deze CT scans werden ook gebruikt voor het vastleggen van de driedimensionale (3D) vervormingen van de wervels. In een eerste serie experimenten werd een duidelijke daling in de gemeten kracht ($>10 - 15\%$ daling t.o.v. maximale kracht) gebruikt als faalcriterium. Het bleek echter dat deze methode onvoldoende resulteerde in het gericht laten falen van de middelste wervels. Daarom werd er een nieuw faalcriterium gekozen. In een tweede serie experimenten werden de proefstukken minimaal 5 mm ingedrukt. Dit nieuwe criterium vergrootte de kans op het induceren van breuken in de middelste wervels. Vervolgens bepaalden we de botsterkte van de proefstukken uit de tweede serie experimenten waarin enkel de middelste wervel was gebroken.

Om vast te kunnen stellen of nieuwe methoden voor het inschatten van wervelinstabiliteit, zoals de SINS score of EE modellen, de klinische praktijk verbeteren, moet er bepaald worden hoe goed artsen deze inschatting momenteel kunnen maken. Daarom had **Hoofdstuk 5** als doel vast te stellen hoe accuraat ervaren artsen de sterkte van wervels met gesimuleerde metastasen kunnen voorspellen en welk type medische beeldvorming - 'magnetic resonance imaging' (MRI), CT en/of 'dual energy X-ray absorptiometry' (DEXA) - hiervoor het meest geschikt is. Vier ervaren artsen kregen opdracht om de wervels getest in Hoofdstuk 4 op volgorde van zwak naar sterk te zetten

op basis van verschillende opeenvolgende sets medische beeldvorming (MRI, CT en/of DEXA). Hun rangschikking vergeleken we vervolgens met de experimentele resultaten. Hierbij zagen we niet alleen dat er grote verschillen waren in hoe goed de verschillende artsen de juiste rangorde konden aangeven ($\tau = 0,111$ ($p > 0,05$) - $0,778$ ($p < 0,01$)), maar zagen we ook dat de artsen de taak zeer inconsistent uitvoerden, zelfs wanneer ze dezelfde beeldvorming tot hun beschikking hadden. Dit impliceert mogelijk dat artsen hun eigen ervaring en strategieën inzetten om een inschatting te maken van de botsterkte, maar ook dat ze gedurende de tijd wisselende methoden gebruiken. Dit zou kunnen leiden tot variaties in de behandeling van patiënten met wervelmetastasen in de klinische praktijk. Deze studie liet tevens grote verschillen zien met betrekking tot de verschillende typen beeldvorming, waardoor er geen antwoord gegeven kon worden op de vraag welk type beeldvorming het meest geschikt is voor het inschatten van wervelsterkte. Wel concludeerden we dat de bevindingen vragen om een meer objectieve methode voor het vaststellen van wervelsterkte.

Hoofdstuk 6 beschreef de ontwikkeling en validatie van subject-specifieke niet-lineaire EE modellen om het faalgedrag te voorspellen van drie opeenvolgende wervels. Het faalgedrag werd hierbij gedefinieerd als (1) welk van de drie wervels werd voorspeld als zwakste; (2) de 3D deformatie van de wervels; (3) stijfheid en (4) faalkracht. Daarnaast werd het effect van gebruik van verschillende materiaalmodellen (wiskundige vergelijkingen tussen botdichtheid en mechanische eigenschappen) op de voorspelling van faalgedrag onderzocht. Van de experimenten beschreven in Hoofdstuk 4 werden EE modellen gemaakt. De boteigenschappen kenden we toe middels vier veelgebruikte materiaalmodellen. In 11 van de 12 geteste proefstukken kon het EE model correct voorspellen welke wervel er gebroken was tijdens het experiment. De voorspelling van de 3D deformatie was echter wat minder veelbelovend bij wervels waarbij de eindplaten gefaald hadden tijdens het experiment. Hoewel de stijfheid van de gehele proefstukken goed voorspeld kon worden door het EE model ($R^2 = 0,637 - 0,688$; $p < 0,01$), was de gevonden correlatie tussen voorspelde en experimenteel gemeten faalkracht zwak ($R^2 = 0,219 - 0,247$; $p > 0,05$). Daarnaast was de correlatie tussen voorspelde en gemeten stijfheid sterk afhankelijk van het gebruikte materiaalmodel. Dit gold echter niet voor de correlatie tussen voorspelde en gemeten faalkracht. Concluderend, in de huidige vorm kan het ontwikkelde EE model gebruikt worden om de zwakste wervel binnen een proefstuk te identificeren maar moeten er nog substantiële verbeteringen doorgevoerd worden voordat het EE model gebruikt kan worden voor het voorspellen van het faalgedrag.

Desalniettemin liet **Hoofdstuk 7** een eerste toepassing van de 'workflow' voor het genereren van EE modellen op patiëntendata zien. Het doel van deze verkennende studie was om te laten zien dat het modelleren van fysiologische belastingen in plaats van een simpele axiale compressiebelasting de voorspelling van het faalgedrag kan beïnvloeden. De patiënt in deze studie had een osteolytische metastase in de vierde lumbale wervel (L4) en kreeg te maken met een pathologische fractuur, 11 maanden na

behandeling met radiotherapie. Van de L3-L5 wervels werd een EE model gemaakt volgens de methode beschreven in Hoofdstuk 6 (simpele axiale compressiebelasting). Vervolgens werden er meer fysiologische belastingscondities opgelegd. De compressie- en afschuifkrachten die in het L2-L3 gewricht optreden tijdens 45° flexie, 90° flexie, 15° extensie, 15° zijwaartse buiging naar rechts en 15° zijwaartse buiging naar links werden berekend met behulp van een spierskeletmodel (Twente Spine Model). Deze krachten werden aangebracht op het EE model. De resultaten lieten zien dat, behalve flexie, geen van de fysiologische belastingscondities leidde tot plasticiteit in L4. Daarnaast was de totale gewrichtsreactiekracht bij 45° flexie aanzienlijk lager dan de reactiekracht die nodig was om een gelijke mate van plasticiteit te induceren bij axiale compressie. Dit kan duiden op het feit dat de betreffende L4 zwakker is wanneer deze in flexie wordt belast dan wanneer deze in compressie wordt belast. Deze verkennende studie was een eerste stap richting het toepassen van de workflow in klinische praktijk. Deze poging tot het combineren van spierskelet- en EE modellen liet zien dat de manier van belasten de voorspelling van het faalgedrag beïnvloedt. Dit impliceert dat er verschillende belastingscondities in acht moeten worden genomen wanneer men overgaat tot het voorspellen van fractures *in vivo*. Echter moeten er nog substantiële verbeteringen in het EE model, het spierskeletmodel en in de combinatie van beide doorgevoerd worden alvorens deze gebruikt kunnen worden voor het voorspellen van het faalgedrag bij fysiologische belastingscondities bij patiënten met wervelmetastasen.

Vervolgens hebben we onderzocht of niet-invasieve behandelingen, als tegenhanger van de instantaan stabiliserende maar invasieve chirurgische behandelingen, botweefsel kunnen stabiliseren. **Hoofdstuk 8** beschreef een systematische literatuurstudie naar het effect van (1) radiotherapie; (2) radiotherapie in combinatie met bisfosfonaten en (3) radiotherapie in combinatie met 'receptor activator of nuclear factor kappa- β ligand' (RANKL) remmers op de botkwaliteit en -sterkte bij botmetastasen afkomstig van solide tumoren. Door middel van zoektermen voor botmetastasen, radiotherapie, bisfosfonaten, RANKL remmers, botdichtheid, botkwaliteit en botsterkte werden Pubmed, EMBASE en de Cochrane Library doorzocht. Studies met zowel mensen als dieren waarbij een willekeurig type en dosis van radiotherapie, bisfosfonaten en RANKL remmers gebruikt werden, konden geïnccludeerd worden. Binnen deze literatuurstudie focusten we op biomechanische uitkomstmaten: re-mineralisatie, botdichtheid, micro-architectuur van bot, botsterkte en pathologische fractures. Van de 3273 verkregen zoekresultaten werden 39 studies (3 dierstudies; 36 humane studies) geïnccludeerd. Hoewel radiotherapie een bewezen effectieve behandeling voor pijn is bij patiënten met botmetastasen en er in de klinische praktijk vele casussen aangewezen kunnen worden waarbij er op medische beeldvorming, gemaakt na radiotherapie, re-mineralisatie te zien is, werd er in deze systematische literatuurstudie onvoldoende bewijs gevonden voor een positief effect van radiotherapie op botkwaliteit en -sterkte. Wel lieten dierstudies zien dat het toevoegen van bisfosfonaten aan de behandeling met radiotherapie leidde tot herstel van botkwaliteit en -sterkte, maar werd dit niet aangetoond in studies met

mensen. Daarnaast waren er geen studies die het effect van het toevoegen van RANKL remmers aan de behandeling met radiotherapie op botkwaliteit en -sterkte onderzocht hebben. Deze systematische literatuurstudie concludeerde dat, hoewel het gepaard gaat met verschillende methodologische, praktische en ethische uitdagingen, er gerandomiseerde studies nodig zijn om het effect van radiotherapie op re-mineralisatie en botsterkte beter te kunnen bepalen.

Hoofdstuk 9 verwoordt een reflectie op het werk zoals beschreven in dit proefschrift en beschrijft toekomstige uitdagingen om het vaststellen van wervelinstabiliteit bij patiënten met wervelmetastasen verder te verbeteren.



12

Dankwoord



Curriculum Vitae



List of publications



PhD portfolio

Curriculum Vitae

Karlijn Groenen was born on February 26th, 1989 in Weert, the Netherlands. In 2007, she obtained her athenaeum diploma from the Philips van Horne Scholengemeenschap in Weert, after which she started studying Biomedical Sciences at the Radboud University in Nijmegen. In 2010, she obtained her Bachelor's degree (*cum laude*) and received the Bex Prize for the best Bachelor's Internship. Subsequently, she enrolled in the Master program Biomedical Sciences. As a part of her Master and to broaden and deepen her knowledge in (bio)medical engineering, she spent a year taking courses at the Faculty of Biomedical Engineering, Eindhoven University of Technology. At the same faculty, Karlijn performed her Master's internship in the Soft Tissue Biomechanics and Engineering Group under supervision of Prof. Cees Oomens and Chen-Ket Chai, PhD. With this thesis, she obtained her Master's degree in Biomedical Sciences *summa cum laude*.

During graduation, Karlijn participated in the Radboud university medical center PhD Competition and received a scholarship to start a PhD project of her own design. This project commenced December 2013 at the Orthopaedic Research Lab of the Radboud university medical center, Nijmegen. Her work focused on improving the assessment of spinal (in)stability in metastatic bone disease.

In addition to her research activities, Karlijn has been a member, secretary, and chair of the Radboud Institute for Health Sciences PhD Council.

Karlijn is currently appointed as a data manager at the Research Bureau of the Department of Radiology and Nuclear Medicine (Radboud university medical center).

List of publications

- Groenen KHJ**, van der Linden YM, Brouwer T, Dijkstra PDS, de Graeff A, Algra PR, Kuijlen JMA, Minnema MC, Nijboer C, Poelma DLH, Rolf C, Sluis T, Terheggen MAMB, van der Togt-van Leeuwen ACM, Bartels RHMA, Taal W. The Dutch national guideline on metastases and hematological malignancies localized within the spine; a multidisciplinary collaboration towards timely and proactive management. *Cancer Treat Rev*, under review.
- Groenen KHJ**, Bitter T, van Veluwen TCG, van der Linden YM, Verdonschot N, Tanck E, Janssen D. Case-specific non-linear finite element models to predict failure behavior in 3-segment spinal units. *J Orthop Res*, under review.
- Groenen KHJ**, van der Linden YM, de Rooy JWI, Sprengers AMJ, Bartels RHMA, Hosman AJF, Tanck E. Assessing spinal instability in metastatic bone disease: Comparing experimentally determined vertebral bone strength with predictions by experienced clinicians. *BMC Musculoskelet Disord*, submitted.
- Groenen KHJ**, Janssen D, van der Linden YM, Kooloos JGM, Homminga J, Verdonschot N, Tanck E. How to induce targeted failure in cadaveric testing of metastatically affected 3-segment spinal units? The importance of a clear and reliable failure criterion. *Med Eng Phys*. 2018;51:104-110.
- Bayoglu R, Geeraedts L, **Groenen KHJ**, Verdonschot N, Koopman B, Homminga J. Twente Spine Model: A Complete and Coherent Dataset for Musculo-Skeletal Modeling of the Thoracic and Cervical Regions of the Human Spine. *J Biomech*. 2017;58:52-63.
- Bayoglu R, Geeraedts L, **Groenen KHJ**, Verdonschot N, Koopman B, Homminga J. Twente Spine Model: A Complete and Coherent Dataset for Musculo-Skeletal Modeling of the Lumbar Region of the Human Spine. *J Biomech*. 2017;53:111-119.
- Bollen L, **Groenen KHJ**, Pondaag W, Van Rijswijk CSP, Fiocco M, Van der Linden YM, Dijkstra PDS. Clinical evaluation of the Spinal Instability Neoplastic Score in patients treated with radiotherapy for symptomatic spinal bone metastases. *Spine* 2017;42(16):E956-E962.
- Groenen KHJ**, Pouw M, Hannink G, Hosman AJF, Van der Linden YM, Verdonschot N, Tanck E. The effect of radiotherapy, and radiotherapy combined with bisphosphonates or RANK ligand inhibitors on bone quality in bone metastases. A systematic review. *Radiotherapy and Oncology*. 2016;119(2):194-201.
- Altmann VC, Groen BE, **Groenen KHJ**, Vanlandewijck YC, van Limbeek J, Keijsers NL. Construct Validity of the Trunk Impairment Classification System in Relation to Objective Measures of Trunk Impairment. *Arch Phys Med Rehabil*. 2016;97(3):437-44.
- Rood A, Hannink G, Lenting A, **Groenen KHJ**, Koëter S, Verdonschot N, van Kampen A. Patellofemoral Pressure Changes After Static and Dynamic Medial Patellofemoral Ligament Reconstructions. *Am J Sports Med*. 2015;43(10):2538-44.

Peer-reviewed conference abstracts

- Groenen KHJ**, van der Linden YM, de Rooy JWI, Sprengers AMJ, Verdonschot N, Bartels RHMA, Hosman AJF, Tanck E. Het bepalen van stabiliteit bij wervelmetastasen: door klinici voorspelde botsterkte versus experimenteel gemeten botsterkte. Najaarsvergadering Nederlandse Orthopedie Vereniging, 2017, Veldhoven, Nederland.
- Groenen KHJ**, van der Linden YM, de Rooy JWI, Sprengers AMJ, Bartels RHMA, Hosman AJF, Tanck E. How good are clinicians in assessing the strength of metastatically affected vertebrae? European Society of Biomechanics, 2017, Seville, Spain.

- Bollen L, **Groenen KHJ**, Pondaag W, van Rijswijk CSP, Fiocco M, van der Linden YM, Dijkstra PDS. Evaluation of the Spinal Instability Neoplastic Score for spinal metastases. European Society for Radiotherapy and Oncology, 2017, Vienna, Austria.
- Bayoglu R, Geeraedts L, **Groenen KHJ**, Verdonschot N, Koopman B, Homminga J. A complete and coherent musculo-skeletal dataset for the thoracic and cervical regions of the human spine. European Society of Biomechanics, 2017, Seville, Spain.
- Bayoglu R, Geeraedts L, **Groenen KHJ**, Verdonschot N, Koopman B, Homminga J. A complete and coherent musculo-skeletal dataset for the human spine. International Society of Biomechanics, 2017, Brisbane, Australia.
- Groenen KHJ**, Janssen D, van der Linden YM, Hosman AJF, de Rooy JWW, Kooloos JGM, Homminga J, Verdonschot N, Tanck E. How to induce targeted failure in experimental testing of 3-segment spinal units. Dutch Bio-Medical Engineering Conference, 2017, Egmond aan Zee, The Netherlands.
- Bayoglu R, Geeraedts L, **Groenen KHJ**, Verdonschot N, Koopman B, Homminga J. Are left-right symmetrical musculo-skeletal models realistic? Dutch Bio-Medical Engineering Conference, 2017, Egmond aan Zee, The Netherlands.
- Groenen KHJ**, Bollen L, Pondaag W, van Rijswijk CSP, Fiocco M, van der Linden YM, Dijkstra PDS. Clinical evaluation of the Spinal Instability Neoplastic Score in 110 patients treated with radiotherapy for symptomatic spinal bone metastases. Eurospine, 2016, Berlin, Germany.
- Dijkstra PDS, **Groenen KHJ**, Pondaag W, van Rijswijk CSP, Fiocco M, van der Linden YM, Bollen L. Limited predictive value of the Spinal Instability Neoplastic Score for spinal instability after evaluation in 110 patients treated with radiotherapy for symptomatic spinal bone metastases. European Musculo-Skeletal Oncology Society, 2016, La Baule-Nantes, France.
- Groenen KHJ**, Janssen D, van der Linden YM, Hosman AJF, de Rooy JWW, Kooloos JGM, Homminga J, Verdonschot N, Tanck E. Clear drop in force does not necessarily indicate vertebral failure in 3-segment spinal units. European Society of Biomechanics, 2016, Lyon, France.
- Bayoglu R, Geeraedts L, **Groenen KHJ**, Verdonschot N, Koopman B, Homminga J. How valid are left-right symmetrical musculo-skeletal models? European Society of Biomechanics, 2016, Lyon, France.
- Groenen KHJ**, Pouw MH, Hannink G, Hosman AJF, van der Linden YM, Verdonschot N, Tanck E. The Effect Of Radiotherapy, And Radiotherapy Combined With Bisphosphonates Or RANK Ligand Inhibitors On Bone Quality In Bone Metastases. A Systematic Review. Annual Meeting of the Orthopaedic Research Society, 2016, Lake Buena Vista, Florida, United States of America.
- Altmann VC, Groen BE, **Groenen KHJ**, Vanlandewijck Y, Keijsers NLW. The new trunk classification system for wheelchair rugby athletes evaluated with dynamic sitting balance measures. International Convention on Science, Education and Medicine in Sport, 2012, Glasgow, United Kingdom.
- Derikx LC, **Groenen KHJ**, van Bon GA, van der Linden YM, Snyers A, Verdonschot N, Tanck E. Patient-specific Finite Element Models Discriminate between Patients with and without a Pathological Fracture in Metastatic Bone Disease. International Society of Biomechanics, 2011, Brussels, Belgium.
- Derikx LC, **Groenen KHJ**, van Bon GA, van der Linden YM, Snyers A, Verdonschot N, Tanck E. Patient-specific Finite Element Models Discriminate between Patients with and without a Pathological Fracture in metastatic Bone Disease. 57th Annual Meeting of the Orthopaedic Research Society, 2011, Long Beach, California, United States of America.

PhD portfolio



Name PhD candidate:	K.H.J. Groenen, MSc	PhD period:	01-12-2013 / 31-11-2017
Department:	Orthopaedic Research Lab	Promotor:	Prof. dr. ir. N. Verdonchot
Graduate School:	Radboud Institute for Health Sciences	Co-promotors:	Dr. E. Tanck Dr. Y.M. van der Linden

TRAINING ACTIVITIES		
	Year(s)	ECTS
a) Courses & Workshops		
RIHS Introduction Course	2014	1.0
Management voor Promovendi	2014	3.0
Presentation Skills	2014	1.5
Systematic Review	2014	0.4
Certificate of Proficiency in English	'14-'15	5.1
Scientific Integrity	2015	1.0
Introductie Nijmeegse Curricula	2015	0.2
Uitvoeringsvaardigheden 1: Werkgroepen begeleiden	2015	0.8
BROK course	2017	1.4
Loopbaanmanagement voor promovendi	2017	0.8
Solliciteren en Netwerken	2017	1.0
b) Seminars & lectures		
Spinoza Lecture Prof. Hoskin	2014	0.1
ESB pre-course on Mimics and Tri-matic	2015	0.25
Onderwijsdag palliatieve zorg radiotherapeuten	2015	0.25
c) Symposia & congresses (OP/ PP indicates oral or poster presentation)		
RIHS Science Day, Nijmegen, The Netherlands	2014	0.25
RIHS PhD Retreat, Wageningen, The Netherlands	2014	0.5
Symposium botmetastasen, UMC Utrecht	2015	0.25
Congress of the European Society of Biomechanics, Prague, CZ	2015	0.75
RIHS PhD Retreat, Wageningen, The Netherlands	2015	0.5
Annual meeting of the Orthopaedic Research Society, Orlando, USA (PP)	2016	1.5
Congress of the European Society of Biomechanics, Lyon, France (OP)	2016	1.25
EUROSPINE, Berlin, Germany (E-PP)	2016	1.25
Dutch Bio-Medical Engineering Conference, Egmond aan Zee, The Netherlands (OP)	2017	1.0
Congress of the European Society of Biomechanics, Seville, Spain (OP)	2017	1.25
Najaarsvergadering Nederlandse Orthopedie Vereniging, Veldhoven, The Netherlands (OP)	2017	0.5
d) Other		
Journal club Orthopaedic Research Lab	'13-'15	2
Lab lunches Orthopaedic Research Lab	'13-'17	3

Continued

TEACHING ACTIVITIES		
	Year(s)	ECTS
e) Lecturing		
BSc course 5DT03 - Determinanten 3: Fysische Factoren	'14-'16	1.8
BSc course MIN05 - Moving Questions	'15-'17	0.5
BSc course 6MBB - Belasting en belastbaarheid	2016	0.4
MSc course 5HM02 - Tissue: Biomechanics and Engineering	'14-'16	7.5
MSc course BMS53 - Biomechanics in Motion	2017	1.2
f) Supervision of internships / other		
BSc internship		
Liset Vliegen, UT Enschede	2014	0.25
MSc internships		
Yan Jiang, UT Enschede	2015	3.0
Remco Doodkorte, RU Nijmegen	2016	0.25
Tristia van Veluwen, UT Enschede	2017	3.0
Pablo Cop, UT Enschede	2017	1.0
Anneke Sloet, RU Nijmegen	2017	1.0
Science Project Biomedical Sciences and Medicine, RU Nijmegen		
Inger Albeda, Miriam Boot, Nadiëh Jansen	'16-'17	1.0
Other		
Liselot van Erp, RU Nijmegen	2016	0.5
OTHER		
RIHS PhD Council - Workshop and Retreat committee	2014	0.25
RIHS PhD Council - Secretary	2015	1
RIHS PhD Council - Chair	2016	1
Co-organizing a 2-day PhD Retreat	2014	2
Review scientific publication (2x)	2015	0.2
TOTAL		57.55

